Marketed Unapproved Drugs Workshop

January 9, 2007

Marketed Unapproved Drugs Workshop
January 9, 2007
8:30 AM - 4:30 PM
Universities at Shady Grove Conference Center
9640 Gudelsky Drive, Auditorium - Bldg. 1, Rockville, MD

8:30	Conference Introduction *Deborah M. Autor, Esq.* *Director, Office of Compliance*
8:30-8:45	Opening Remarks *Andrew C. von Eschenbach, M.D.* *Commissioner, Food & Drug Administration*
8:45-9:00	Welcome *Steven K. Galson, M.D., M.P.H.* *Director, Center for Drug Evaluation and Research*
9:00-9:15	Overview of the "Unapproved Universe" *Deborah M. Autor, Esq.* *Director, Office of Compliance*
9:15-9:35	Regulatory Pathway: OTC Monograph *Reynold Tan, Ph.D.* *Interdisciplinary Scientist, Division of Nonprescription Regulation Development, Office of Nonprescription Products*
9:35-10:00	Chemistry, Manufacturing, and Controls Requirements *Moheb M. Nasr, Ph.D.* *Director, Office of New Drug Quality Assessment*
	Break
10:15-10:45	Regulatory Pathway: ANDA *Gary Buehler* *Director, Office of Generic Drugs*
10:45-11:05	Regulatory Pathway: NDA Process *Kim Colangelo* *Associate Director for Regulatory Affairs, Office of New Drugs*
11:05-11:45	NDA/Demonstrating Product Effectiveness *Robert Temple, M.D., Director, Office of Medical Policy and Acting Director, Office of Drug Evaluation I*
11:45-12:30	Question & Answer Session

12:30-1:45 Lunch

1:45-2:15 NDA/Demonstrating Product Safety
(pre-clinical and clinical requirements)
John Jenkins, M.D.
Director, Office of New Drugs

David Jacobson-Kram, Ph.D., DABT
Associate Director for Pharmacology and Toxicology,
Office of New Drugs

Robert J. Meyer, M.D.
Director, Office of Drug Evaluation II

2:15-2:30 Pediatric Research Equity Act: Pediatric Considerations
Lisa Mathis, M.D.
Associate Director, Pediatrics and Maternal Health Staff,
Office of New Drugs

2:30-3:00 Patent and Non-Patent Exclusivities
Kim Dettelbach
Office of the General Counsel

3:00-3:15 User Fees & Waivers
Mike Jones
Special Assistant, Office of Regulatory Policy

3:15-3:25 Role of the Unapproved Drugs Coordinator
Sally Loewke, M.D.
Assistant Director for Guidance & Policy and
Unapproved Drugs Coordinator, Office of New Drugs

Break

3:45-4:30 Question and Answer Session

4:30 Closing

Introductions for the Marketed Unapproved Drugs Workshop
(in order of the workshop presentations)

Opening Remarks
Andrew C. von Eschenbach, MD – Commissioner
U.S. Food & Drug Administration

Dr. von Eschenbach was sworn in as the 20th Commissioner of the U.S. Food and Drug Administration on December 13, 2006. As the former Director of the National Cancer Institute at the National Institutes of Health, he is a nationally recognized urologic surgeon and oncologist. He has held several prominent positions at University of Texas, MD Anderson Cancer Treatment Center in Houston. Dr. von Eschenbach has been a distinguished leader in the field of cancer research and progressive patient care for over 30 years. We are honored that his many accomplishments, expertise and vast experience have brought him here to head the FDA.

Welcome
Steven K. Galson, MD, MPH – Director
Center for Drug Evaluation & Research (CDER)

US Public Health Service, Rear Admiral (RADM) Steven Galson was named Director of the Center for Drug Evaluation and Research (CDER) in July, 2005. He provides leadership for the Center's broad national and international programs in pharmaceutical regulation. Dr. Galson joined FDA in April 2001 as the CDER Deputy Director after holding senior level positions at the Environmental Protection Agency, the Department of Energy where he was the Chief Medical Officer, and the Department of Health and Human Services.. Dr. Galson is an Internal medicine physician, Board Certified in Preventive Medicine & Public Health and Occupational Medicine.

Overview of Unapproved Universe: Legal & Medical
Deborah M. Autor, Esq. – Director
Office of Compliance

Deborah Autor is the Director of CDER's Office of Compliance. She has been with FDA since 2002 and previously served as Associate Director for Compliance Policy in the Office of Compliance. Before joining FDA, Ms. Autor was a Trial Attorney for seven years at the Office of Consumer Litigation of the Department of Justice, where she litigated civil and criminal cases on behalf of FDA. Before that, Ms. Autor was an attorney in private practice, where she specialized in counseling FDA-regulated companies. The Office of Compliance advances CDER's mission of assuring that safe and effective drugs are available to the American people by protecting Americans from unsafe and ineffective drugs.

Regulatory Options: OTC Monograph
Reynold Tan, PhD – Interdisciplinary Scientist
Office of Nonprescription Products

Dr. Tan received his Bachelor's Degree in Biochemistry from the University of Pennsylvania and a Ph.D in Biochemistry from the University of Maryland. Prior to coming to FDA, he worked for 5 years as a research chemist for Knoll Pharmaceutical Company. Dr. Tan has been an Interdisciplinary Scientist in the Office of Nonprescription Products at FDA since 2002.

Chemistry, Manufacturing, and Controls Requirements
Moheb Nasr, PhD – Director
Office of New Drug Quality Assessment

ONDQA is responsible for quality assessments of new drugs, pre and post marketing, regulated by CDER. Dr. Nasr serves as the FDA lead at the International Conference on Harmonization (ICH) Q8 Expert Working Group and is a member of FDA's Council on Pharmaceutical Quality. After a distinguished academic career, Dr. Nasr joined the FDA in 1990.

Regulatory Options: ANDA
Gary Buehler, RPH – Director
Office of Generic Drugs

Mr. Buehler is a pharmacist and was appointed Director of OGD in July of 2001, after serving as the Deputy Director of that office since 1999. Mr. Buehler has worked for FDA since 1986. Prior to joining the Office of Generic Drugs, he was a Senior Regulatory Project Manager in the Division of Cardio-Renal Drug Products.

Regulatory Options: NDA Process
Kim Colangelo – Associate Director of Regulatory Affairs
Office of New Drugs

Ms. Colangelo is responsible for providing guidance on regulatory, scientific, policy, and administrative matters in the Office of New Drugs, and serves as the leader for two teams of project managers providing regulatory support for initiatives within OND and the Center. She has worked for the FDA since 1996.

NDA/Demonstrating Product Efficacy
Robert Temple, MD – Director, Office of Medical Policy *and*
Acting Director, Office of Drug Evaluation I

The Office of Medical Policy is responsible for assessing quality of clinical trials and for regulation of industry promotional materials through the Division of Drug Marketing, Advertising, and Communication (DDMAC). ODE I is responsible for the regulation of cardio-renal, neuropharmacologic and psychopharmacologic products. Dr. Temple has been with FDA for 34 years and spent about a decade as final CDER sign-off on DESI drugs. He has a long standing interest in design of clinical trials and assessment of evidence.

NDA Demonstrating Product Safety

John K. Jenkins, MD – Director
Office of New Drugs

Dr. Jenkins is currently the Director of the Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration. Dr. Jenkins joined FDA as a medical officer in the Division of Oncology and Pulmonary Drug Products in 1992. He subsequently served as Pulmonary Medical Group Leader and Acting Division Director before being appointed as Director of the newly created Division of Pulmonary Drug Products in 1995. Dr. Jenkins became the Director of the Office of Drug Evaluation II in 1999 and served in that position until he was appointed to his current position in January 2002. Dr. Jenkins is Board Certified in Internal Medicine and Pulmonary Diseases.

Robert Meyer, MD – Director, Office of Drug Evaluation II *and*
Acting Director, Office of Drug Evaluation I

Dr. Meyer has been the Director of Office of Drug Evaluation II since 2002. The ODE is responsible for the regulation of endocrine/metabolic, pulmonary, allergy, rheumatologic, analgesic and anesthetic products. He is involved in a number of Center and Agency level activities such as chairing the Agency's Risk Assessment Guidance working group and the Drug Safety Oversight Board. Dr. Meyer began his career with FDA in 1994.

David Jacobson-Kram, PhD – Associate Director of Pharmacology and Toxicology,
Office of New Drugs

Dr. Jacobson-Kram joined the Office of New Drugs in 2003. Prior to FDA, he has worked in the private sector holding such positions as the Vice President of Toxicology and Laboratory Animal Health and serving on the faculties of the George Washington University medical school and the Johns Hopkins University Oncology Center. Throughout his career, Dr. Jacobson-Kram has published extensively on genetic and molecular toxicology.

Pediatric Research Equity Act

Lisa Mathis, MD – Associate Director
Pediatrics and Maternal Health Staff

The Pediatric and Maternal Health Staff function within CDER to consult on pediatric, pregnancy, and lactation issues in clinical protocols, study reports, and labeling. Dr. Mathis is a board certified, practicing pediatrician who joined the FDA as a medical reviewer in 2000.

Exclusivity

Kim Dettelbach
Office of the General Counsel

Ms. Dettelbach is an associate chief counsel in the Food and Drug division of the HHS Office of General Counsel. Her practice concentrates on issues relating to generic drugs and exclusivity, 505(b)(2) NDAs, orphan drugs, and pediatric drug development. She has been with FDA for 8 years.

User Fees & Waivers

Mike Jones – Special Assistant
Office of Regulatory Policy

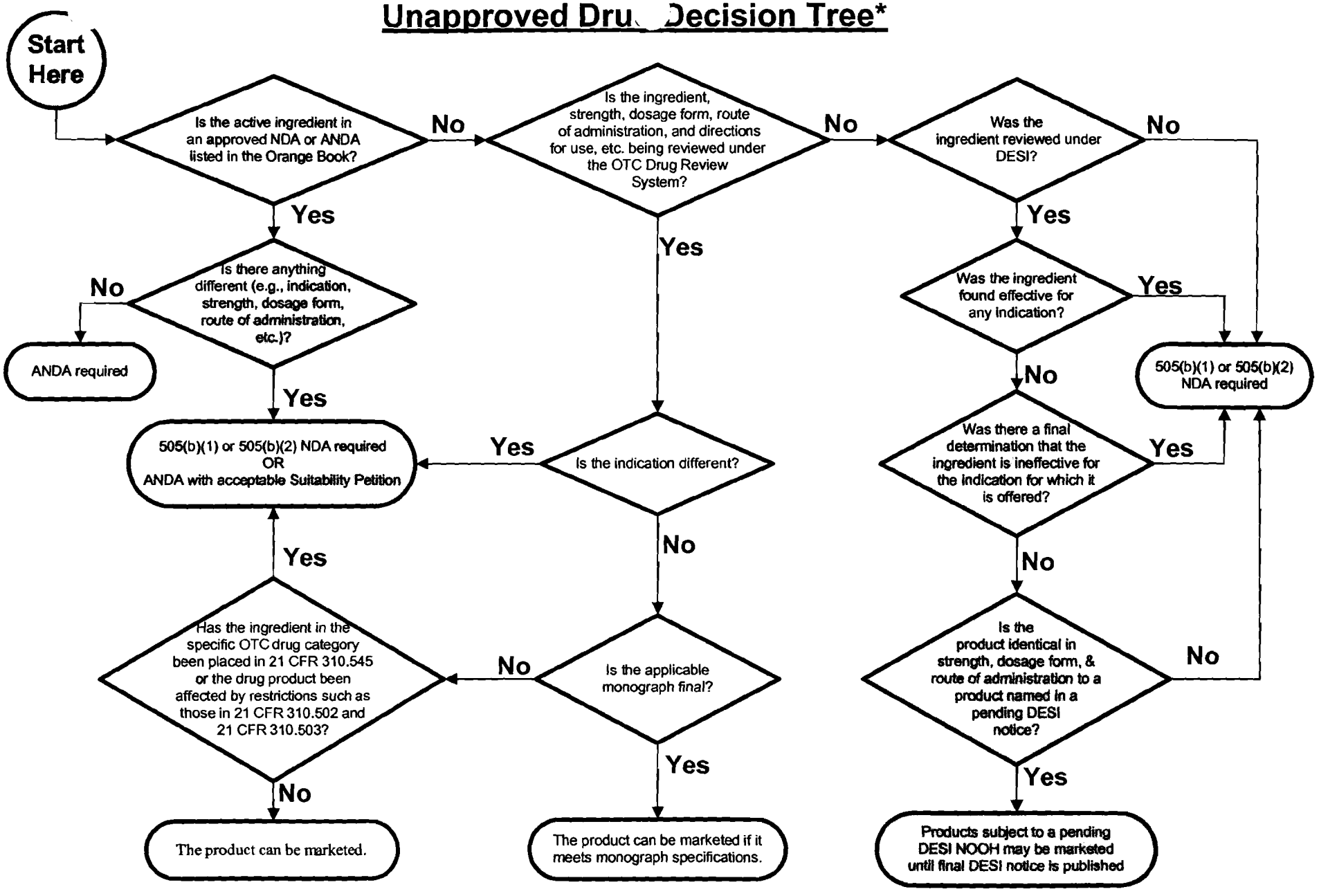
Mike Jones is a pharmacist and has been at FDA for 17 years and with the User Fee program since 1993.

Role of the Unapproved Drugs Coordinator

Sally Loewke, MD – Assistant Director of Guidance & Policy
Unapproved Drugs Coordinator

Dr. Loewke is the Assistant Director for Guidance and Policy in the Office of New Drugs (OND) in the FDA's Center for Drug Evaluation and Research (CDER). In this position, Dr. Loewke works to ensure an efficient standardized review process within OND by aiding in the development and implementation of review policies and procedures. As part of her duties, Dr. Loewke also serves as the Unapproved Drugs coordinator. Dr. Loewke has been with the FDA since 1996.

Unapproved Drug Decision Tree*



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The Unapproved Universe

January 9, 2007

Deborah M. Autor, Esq.
Director,
CDER Office of Compliance

[redacted]

The Unapproved Universe

January 9, 2007
Deborah M. Autor, Esq.
Director,
CDER Office of Compliance

Overview of Presentation

- Why FDA is concerned about unapproved drugs
- Legal description of the "unapproved universe"
- The unapproved drugs initiative: the 2006 CPG ("Marketed Unapproved Drugs - Compliance Policy Guide") and the multi-pronged approach
- Workshop overview

2

Why Is FDA Concerned About Unapproved Drugs?

- Physicians and consumers cannot assume that marketed drugs have been found by FDA to be safe and effective
  - even if those drugs are listed in the Physician's Desk Reference (PDR)
- Potential for drug labeling deficiencies
- Potential for drug quality deficiencies

3

Why Is FDA Concerned About Unapproved Drugs?

- Limited post-market surveillance and no periodic reporting
- In some cases, there may not be a documented safety risk
  - But, the absence of proof of a problem is not proof of the absence of a problem
- Challenge the integrity of the drug approval system
  - Reduce incentives for research to prove safety/effectiveness
  - Inequitable: unapproved drugs compete unfairly with approved ones

4

"Unapproved Universe" Legal Description: Introduction

- FDA estimates that there are several thousand illegal marketed unapproved drugs
- Three main categories of marketed unapproved drugs
  - DESI Drugs
  - Prescription "Wrap-Up"
  - Post '62 Drugs

5

"Unapproved Universe" Legal Description: Details

- DESI Drugs
  - DESI means Drug Efficacy Study Implementation
  - Refers to drugs that were the subject of 1938-1962 NDAs (safety only) and drugs that are identical, related, and similar to such drugs
  - DESI drugs are *not* "grandfathered" or generally recognized as safe and effective (GRAS/E)
- Prescription "Wrap-Up"
  - Refers to drugs that are on the market based on a claim of being a pre-'38 or pre-'62 product or identical, related, or similar to such a product
- Post '62 Drugs
  - Drugs initially marketed after 1962

6

"Unapproved Universe" Legal Description: Bottom Line

- All drugs must have FDA approval or comply with an Over the Counter monograph, unless:
  - DESI pending or OTC monograph pending
    - Less than 20 DESI proceedings pending (out of almost 600)
    - Many OTC monographs have been finalized
  - Generally recognized as safe and effective (GRAS/E)
    - The agency believes it is not likely that any currently marketed prescription drug is GRAS/E
    - For example, a GRAS/E finding requires a consensus among experts that the product is safe and effective based on published scientific literature regarding the finished drug product of the same quality and quantity needed to approve a drug

7

"Unapproved Universe" Legal Description: Bottom Line

- All drugs must have FDA approval or comply with an Over the Counter monograph, unless:
  - Grandfathered
    - The agency believes it is not likely that any currently marketed prescription drug is grandfathered
    - For example, for grandfather status, a firm must document that its product is identical in formulation, strength, dosage form, route of administration, indications, intended patient population, and other conditions of use to a drug marketed on the relevant date for the 1938 or 1962 grandfather clause
    - For the 1962 grandfather clause, the firm must also document that the drug was GRAS in 1962 based on published scientific literature

8

The Unapproved Drugs Initiative: Goals of the 2006 CPG

- Improve the safety of the drug supply by enforcement and by bolstering incentives to submit applications for marketed unapproved drugs
- Encourage companies to comply with the drug approval process, while minimizing disruption to the marketplace
- Provide notice that any product that is being marketed illegally is subject to FDA enforcement action at any time (CPG, page 4)

9

The Unapproved Drugs Initiative: Enforcement Priorities in the CPG

- For all unapproved drugs (DESI, Wrap-Up, Post-62):
  - Drugs with potential safety risks
  - Drugs that lack evidence of effectiveness
  - Fraudulent drugs
  - Unapproved drugs that directly compete with an approved drug
  - Drugs from manufacturers that are otherwise violating the Act
    - Examples: GMP violations, ADE reporting violations
  - Drugs with formulation changes made as a pretext to avoid enforcement

10

The Unapproved Drugs Initiative: Multi-Pronged Approach

- FDA is committed to tackling the unapproved drugs problem
- The agency's multi-pronged approach includes
  - Enforcement
  - Education
  - Incentives
  - Other Measures

11

Workshop Overview: Why

- Product of the CDER/ORA unapproved drugs working group that meets weekly to further this initiative
- Modeled on questions frequently asked by industry
- Intent is to educate, especially small businesses
- We hope that, with education and incentives, companies will take the initiative to get approval, and enforcement will be necessary in fewer cases

12

Workshop Overview: What

- We will talk in generalities today
- Specific scientific questions will need to be addressed to the relevant Division of the Office of New Drugs
- Legal questions can be addressed to the Office of Compliance

13

Workshop Overview: Agenda

- Regulatory Pathways for Legal Marketing
  - OTC Monograph
  - ANDA
  - NDA (505(b)(1) and 505(b)(2))
- Other Important Issues for Applicants
  - Chemistry, Manufacturing, and Controls
  - Pediatric Considerations
  - Exclusivities
  - User Fees and Waivers
  - Role of the Unapproved Drugs Coordinator

14

Workshop Overview: Spectrum of Uncertainty

From

- Active ingredients that are unknown (from FDA's regulatory standpoint), such as
  - New molecule never previously approved

To

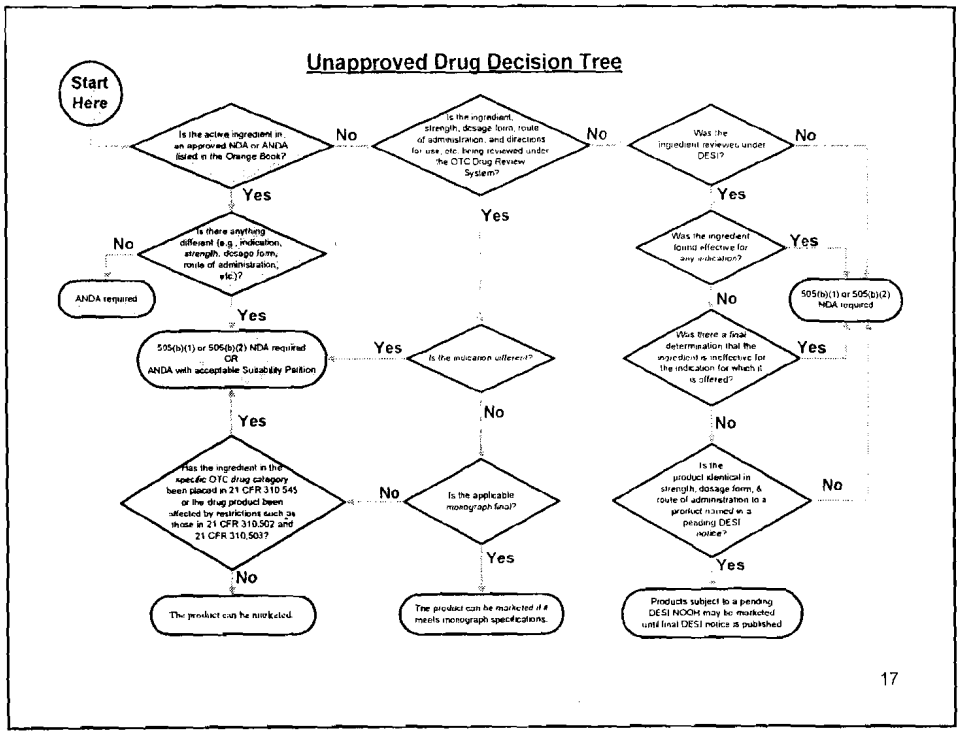
- Active ingredients that are well known, such as
  - Already approved for another firm
  - DESI final effective (or those identical, related, or similar to it)

15

Workshop Overview: Use of the Decision Tree

- Simply a guide
- Will become more clear during the course of the day

16



17

Workshop Overview: Conclusion

- We can only brush the surface today, but we hope this workshop will help manufacturers of unapproved drugs to understand how to comply with the law
- Slides and links to relevant guidances will be posted on the unapproved drugs web page: www.fda.gov/cder/drug/unapproved_drugs

18

Regulatory Pathways: OTC Monograph

Reynold Tan, Ph.D.
Interdisciplinary Scientist
FDA/Office of Nonprescription Products

Regulatory Pathways: OTC Monograph

Reynold Tan, Ph.D.
Interdisciplinary Scientist
FDA/Office of Nonprescription Products

Over-the-counter (OTC) Drugs

- "OTC" drugs = "nonprescription" drugs
- 1951 Durham Humphrey Amendment: Authorized FDA to classify certain drugs as available by prescription only
- FDA's Office of Nonprescription Products (ONP) regulates the marketing of OTC drugs
  - http://www.fda.gov/cder/Offices/OTC/default.htm

Marketing of OTC Drugs in the U.S.

Two regulatory pathways:

- New Drug Application (NDA)
  - FDA "approves" marketing
  - Drug product-specific
- OTC Drug Monograph
  - FDA "allows" marketing (pre-approval not required)
  - Active ingredient/Drug category-specific
  - Developed by the OTC Drug Review

What is an OTC Drug Monograph?

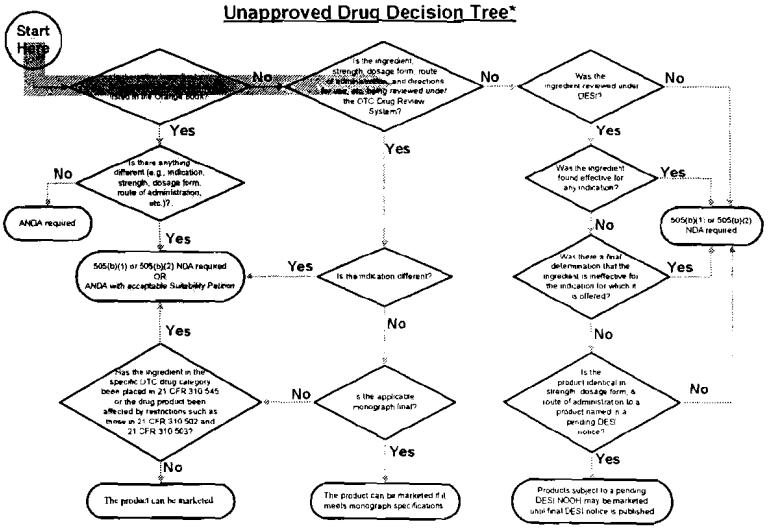
- "Recipe book" for marketing an OTC drug
- GRASE: Generally Recognized As Safe and Effective
  required GRASE conditions → GRASE product
- Final monographs are published in Code of Federal Regulations (CFR)
  - 21 CFR parts 331-358
  - http://www.fda.gov/cder/Offices/OTC/industry.htm

What are the "conditions of use" in an OTC Drug Monograph?

Required GRASE conditions:

- Active ingredients
  - Dosage strength
  - Dosage form
- Labeling requirements
  - Indications
  - Warnings
  - Directions
- Final formulation testing (*sometimes*)

Unapproved Drug Decision Tree*



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6

The OTC Drug Review (Overview in 21 CFR Part 330)

When the OTC Drug Review began in 1972:

- 100,000 to 500,000 marketed OTC drug products
- ~200 OTC active ingredients and ~26 OTC drug categories
  - Active ingredients/drug categories under the OTC Drug Review (See *"OTC Drug Review Ingredient Status Report"* at http://www.fda.gov/cder/Offices/OTC/industry.htm)

OTC Drug Review → OTC Monograph

Three-step public rulemaking process:

1. Advance Notice of Proposed Rulemaking (ANPR)
2. Tentative Final Monograph (TFM)
3. Final Monograph (FM)

Dockets submissions: http://www.fda.gov/ohrms/dockets/default.htm

Status: http://www.fda.gov/cder/otcmonographs/rulemaking_index.htm

OTC Drug Review → OTC Monograph

Advisory Review Panels

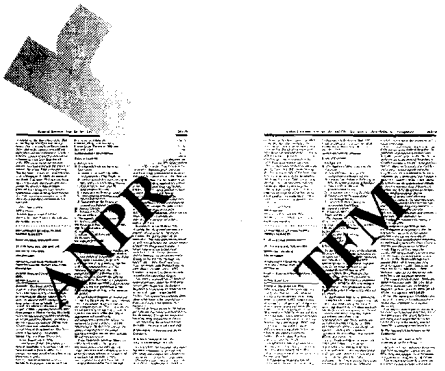
- Category I: GRASE
- Category II: not GRASE
- Category III: cannot determine if safe and effective

OTC Drug Review → OTC Monograph

- Category I: GRASE
- Category II: not GR
- Category III: cannot [illegible] afe and effective

OTC Drug Review → OTC Monograph

Comments



OTC Drug Review → OTC Monograph

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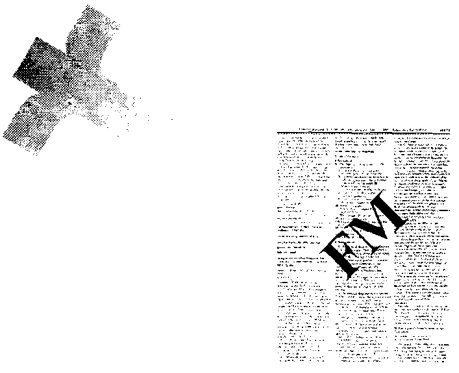
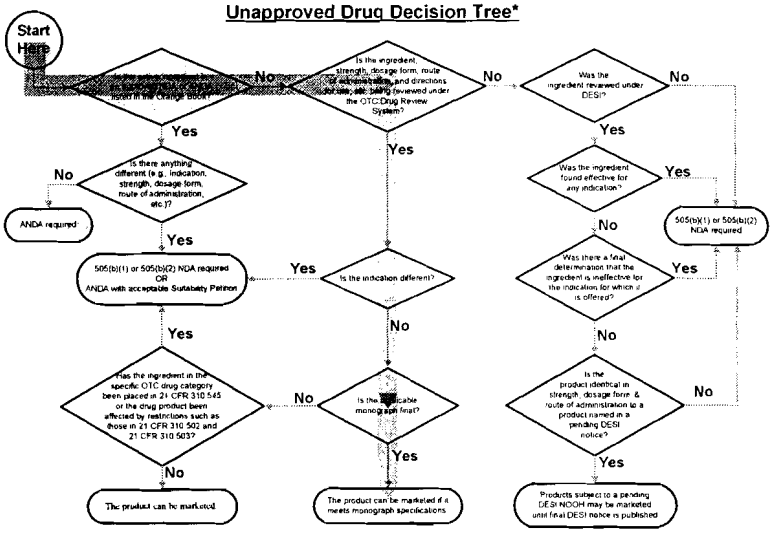


Data

Unapproved Drug Decision Tree*



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13

Example of a Final OTC Drug Monograph: Antacid

§331.10 *Active ingredients*... Calcium, as carbonate or phosphate; maximum daily dosage limit 160mEq. calcium (e.g., 8 grams calcium carbonate)

§331.30(b) *Indications*... "For the relief of" (optional, any or all of the following:) "heartburn," "sour stomach," and/or "acid indigestion"

§331.30(c) *Warnings*... "Do not take more than (maximum recommended daily dosage) in a 24-hour period, or use the maximum dosage of this product for more than 2 weeks,

Drug Facts

Active ingredient(s)	***Purpose***
Calcium carbonate USP 750mg	Antacid

Use(s) relieves ▪acid indigestion ▪heartburn ▪sour stomach

Warnings

Ask a doctor or pharmacist before use if you are taking a prescription drug. Antacids may interact with certain prescription drugs.

When using this product
▪do not take more than 10 tablets in 24 hours
▪do not use the maximum dosage for more than 2 weeks

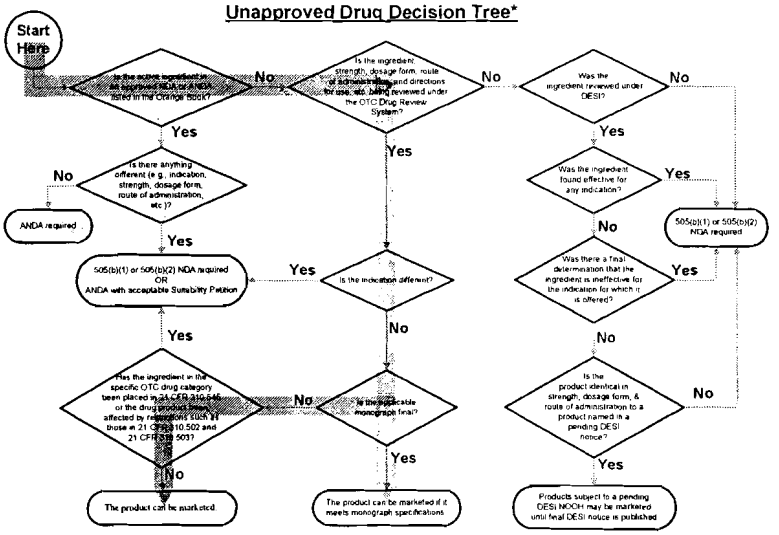
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
chew 2-4 tablets as symptoms occur, or as directed by a doctor

Other information store at room temperature

Inactive ingredients sucrose, corn starch, talc, mineral oil, natural and artificial flavors, adipic acid, sodium polyphosphate, red 40 lake, yellow 6 lake, yellow 5 lake, blue 1 lake

Questions or comments? 1-800-xxx-xxxx



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15

Marketing Drug Products When The Monograph Is Not Final

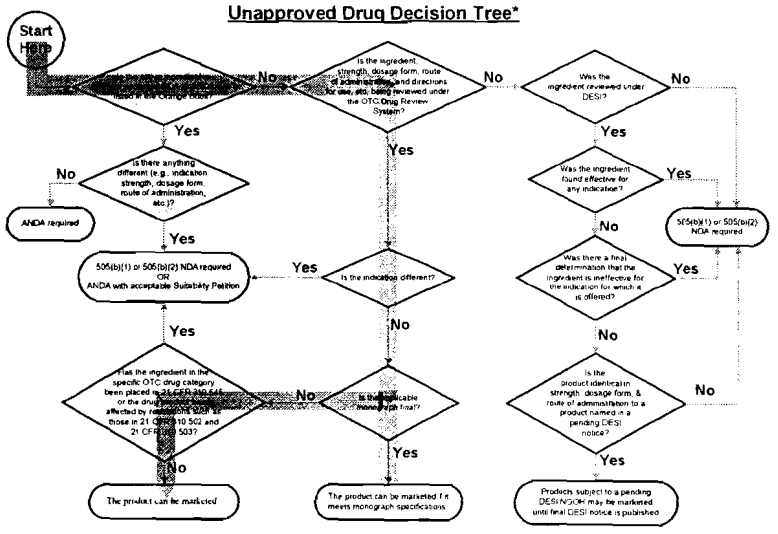
- When the ingredient and indication are (1) under the OTC Drug Review and (2) not in a Final Monograph, the ingredient/indication can be marketed pending completion of the Final Monograph.
  - *Compliance Policy Guide*: 450.200 and 450.300
    - "would not be in the agency's interest to pursue regulatory action unless failure to do so poses a potential health hazard to the consumer"
    - http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg
  - 21 CFR 330.13: Conditions for marketing ingredients recommended for OTC use under the OTC Drug Review
    - Continued marketing is at risk that proposed GRASE conditions may change

Exceptions to Marketing an Ingredient and Indication

21 CFR 310.500s: types of drug products considered new drugs (*i.e.*, require NDA):

Such as:

- 21 CFR 310.545: Specific ingredients in specific OTC drug categories that are not GRASE for OTC drug products
- 21 CFR 310.502(a)(14): Timed-release dosage forms
- 21 CFR 310.503: Irradiated drug products



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18

Marketing a Drug Product That Deviates from a Final Monograph

- NDA Deviation
- Citizen Petition

NDA Deviation

- 21 CFR 330.11
- "monograph deviation",
  "NDA 505(b)(2) that references a final monograph"
- Product meets all conditions of the applicable final monograph except for a deviation
- Submit data in NDA to support safety and effectiveness of product with deviation

NDA Deviation (example)

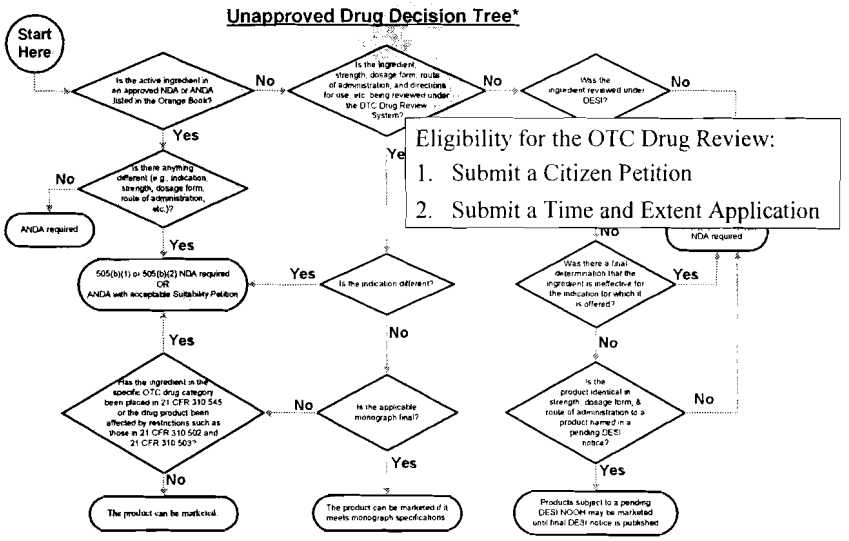
pyrethrins + piperonyl butoxide *aerosol foam*: pediculicide

- FDA: Final monograph for OTC Pediculicide Drugs allows combination in *nonaerosol dosage form* only
- Manufacturer: Product meets conditions of Pediculicide Final Monograph except for its dosage form
  - Referenced safety and effectiveness information in Pediculicide Final Monograph
  - Submitted additional bridging-type studies for safety and effectiveness linking this NDA product to the similar monograph product
  - Submitted new Chemistry, Manufacturing and Control information
- FDA: Approved NDA based on data submitted in this NDA deviation application and the Pediculicide Final Monograph

Citizen Petition

- 21 CFR 10.30
- Can be used to amend OTC drug monograph at any step
- Limited to pre-1975 marketing conditions
  - "conditions": active ingredient, dosage form, indication, etc.
- Must include data or information demonstrating safety and effectiveness
- Cannot market the product with the "new condition" until the Final Monograph is amended

Unapproved Drug Decision Tree*



Eligibility for the OTC Drug Review:

1. Submit a Citizen Petition
2. Submit a Time and Extent Application

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23

Time and Extent Application

- Mechanism to incorporate a "new condition" in a monograph
- 21 CFR 330.14
- Can be used to amend OTC drug monograph at any step
  - OTC drugs with U.S. marketing experience after 1975
  - OTC drugs with marketing experience outside the United States
- Step 1, Eligibility: Meets marketing requirements for "material time" and "material extent" in 21 CFR 330.14(b)
  - >5 continuous years in the same country and "in sufficient quantity"
- Step 2, Safety and Effectiveness Review: FDA reviews safety and effectiveness data to determine GRASE

Time and Extent Application (example of Step 1, TEA eligibility)

climbazole: dandruff shampoo

- FDA: Climbazole not allowed in Dandruff Final Monograph
- Manufacturer: Submitted request for TEA eligibility:
  - Foreign marketing experience
    - Diverse population representative of U.S. population
    - Marketing in an OTC environment
    - Marketing data on number of dosage units sold
- FDA: TEA eligibility demonstrated (*Notice of Eligibility/Call-for-Data* published in Federal Register)
  - http://www.fda.gov/cder/otcmonographs/category_sort/dandruff.htm
- Product still is not covered by final monograph and cannot be marketed until:
  - Data submitted demonstrates safety and effectiveness
  - A USP Monograph is established for climbazole

For More Information

Internet websites:

http://www.fda.gov/cder/Offices/OTC/default.htm (general)
http://www.fda.gov/cder/Offices/OTC/industry.htm (industry)
http://www.fda.gov/ohrms/dockets/default.htm (public dockets)
http://www.fda.gov/cder/otcmonographs/rulemaking_index.htm (monographs)
http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg (compliance guidance)

Email:

Walter Ellenberg: walter.ellenberg@fda.hhs.gov
Leah Christl: leah.christl@fda.hhs.gov

Chemistry, Manufacturing, & Controls (CMC) Requirements

Moheb M. Nasr, Ph.D.
Office of New Drug Quality Assessment
ONDQA, CDER, FDA

Moheb.Nasr@FDA.HHS.GOV

Unapproved Drugs
Workshop
January 9, 2007

Chemistry, Manufacturing, & Controls (CMC) Requirements

Moheb M. Nasr, Ph.D.
Office of New Drug Quality Assessment
ONDQA, CDER, FDA

Moheb.Nasr@FDA.HHS.GOV

Unapproved Drugs Workshop
January 9, 2007

Outline

- General information and references
- CMC Expectations
  - Drug Substance
  - Drug Product
- Additional Considerations

2

References

- Content and format of an application – 21 CFR 314.50
- Guidances (including ICH):
  - http://www.fda.gov/cder/guidance/index.htm
- MaPPs: http://www.fda.gov/cder/mapp.htm
- GMPs: http://www.fda.gov/cder/regulatory/applications/compliance.htm
- Additional helpful information: http://www.fda.gov/cder/regulatory/default.htm#Regulatory

3

General

- ANDA/NDA Submission:
  - Format:
    - CTD recommended but not required
    - Can be either paper or electronic (eCTD)
  - Can reference required information in Drug Master File (DMF)
    - i.e., DMF reference for drug substance, packaging components, excipients
    - Must have appropriate Letter of Authorization (LOA) referencing the location(s) of the information in the DMF/NDA.
    - List of DMF holders: http//www.fda.gov/cder/dmf/
- For NDA, we recommend a pre-submission meeting

4

CMC Expectations

- Full description of the composition, manufacture, and specifications under 21 CFR 314.50(d)(1) and, for ANDAs, 21 CFR 314.94
- Must include Chemistry, Manufacturing, and Controls (CMC) info on:
  - Drug substance
  - Drug product and excipients
  - Packaging components
- Additional information as appropriate (e.g., comparison studies)

5

Drug Substance (DS)

Drug substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body..." [21 CFR 314.3]

6

Drug Substance (DS)*

- Full description of the drug substance
  - Identity, physical, and chemical characteristics, and Stability
  - Method of synthesis (or isolation) and purification, including appropriate selection of starting materials
  - Manufacturing process controls (quality controls)
  - Specifications (including test methods) necessary to ensure purity and drug product performance
  - Level and qualification of impurities**
  - Container closure and stability information
- Name, address, & contact info of manufacturer
- May reference DMF, with appropriate LOA, for this information

*regulation citation: 21 CFR 314.50(d)(1)(ii)
**ICH guidance Q3a&c

7

Drug Substance

- Complexity may depend upon:
  - Sources and methods of preparation
    - Synthesis
      - Chemical, enzymatic
      - Single-step, multi-step, stereo-specific, etc.
    - Fermentation
    - Biotechnology – Recombinant, Transgenic, etc.
  - Naturally derived
    - Animal, botanical, mineral
      - BSE considerations if bovine derived
    - Isolation, extraction, purification, etc.
  - Physico-chemical and thermal stability

8

Drug Substance Stability

- Retest date or expiry assigned based upon data
- Stability testing protocol
  - Stability testing under controlled conditions
    - Accelerated 45°C/75% RH
    - Room Temperature (RT) 25°C/60% RH
  - Tests & acceptance criteria
    - Stability indicating assay
  - Testing frequency
    - ICH Q1A
- Container closure system representative of large bulk container/drum
- Submission expectations
  - For NDAs
    - 3 batches - 6 months RT and accelerated data
    - May statistically project expiry up to 6 months past RT data (trending!)
  - For ANDAs
    - 1 batch - 3 months accelerated
    - 3 months satisfactory accelerated data may permit 24 months expiry

9

Drug Product*

- The marketed dosage form designed to consistently deliver the drug substance at the desired rate
- Complexity may depend upon:
  - Physico-chemical, thermal stability of the formulation components
  - Route of administration
  - Onset of action
  - Site of action
  - Dosage form
  - Drug delivery system

*Regulation citation: 21 CFR 314.3(b)

10

Drug Product (DP)*

- Description & composition/formulation of the DP
  - A list of all components used in the manufacture of the DP, even if removed during manufacturing (e.g., solvents)
  - Composition of the drug product
    - Quantitative composition of drug product
    - List sub-formulations separately (e.g., tablet coating, mixture of IR and MR granules)
    - List tracers
    - Proprietary mixtures such as colors or flavors can be listed by their proprietary name (e.g., DMF)
    - Excipients on the "inactive ingredient list" for the amount and dosage form used do not need to be qualified

*Regulation citation: 21 CFR 314.50(d)(1)(ii)

11

Drug Product (cont.)

- Name, address, & contact info of the DP manufacturer(s)
- Description of the manufacturing & packaging processes, including process controls
- Container closure system
- Sterility assurance for sterile products
  - Guidance:
    - http://www.fda.gov/cder/guidance/old031fn.pdf
    - Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice
- Drug Delivery Systems, if appropriate
  - Modified release dosage forms
  - Transdermal patches
  - Oral inhalation drug products
- Environmental Assessment
  - *Regulation citations: 21 CFR 25.30, 25.31, & 25.40*
  - *Guidance for Industry for the submission of Environmental Assessment for Drug Applications and supplements (Nov. 1995)*

12

Drug Product Stability (shelf life)*

- To establish expiry based upon data
- Stability Protocol
  - Storage Conditions
    - Room temperature (RT) (25°C/60% relative humidity)
    - Accelerated (40°C/75% relative humidity)
  - Tests & acceptance criteria
    - Stability indicating assay
  - Testing frequency
    - ICH Q1A
- Submission expectations
  - For NDAs
    - 3 batches - 6 months RT and accelerated data
    - May statistically project expiry up to 6 months past RT data (trending!)
  - For ANDAs
    - 1 batch - 3 months accelerated
    - 3 months satisfactory accelerated data may permit 24 months expiry

*see ICH guidance Q1

13

Drug Product - Specifications

- Specifications are the quality standards (i.e., tests, analytical procedures, & acceptance criteria) provided in the application to ensure the quality and performance of the DS, DP, intermediates, raw materials, reagents, container closure systems, etc. in order to assure safety and efficacy
- Examples for solid oral dosage forms may include:
  - Appearance
  - Assay/potency
  - In-vitro dissolution or disintegration test
  - Impurity profile
  - Content uniformity
  - Other critical quality attributes, as appropriate
- USP monograph/public standards are considered minimum requirements
  - Additional specifications may be needed (e.g., impurities)

14

Additional considerations

- All facilities used in the manufacture of the drug (i.e., DS, DP, packagers, testers) should be ready for inspection upon submission of the application
- Facilities should operate under Current Good Manufacturing Practices (CGMPs)
  - CGMP Regulations 21 CFR 210 & 211
  - CGMP Guidances http://www.fda.gov/cder/guidance/index.htm#CGMPS-Eff
  - Inspection will evaluate conformance to CGMPs

15

THANK YOU!

For further information, contact ONDQA @ 301-796-1900, or

Michael Folkendt, (301) 796-1670
Michael. Folkendt@FDA.HHS.GOV

16

Regulatory Pathway: Abbreviated New Drug Application

Gary Buehler
Director
Office of Generic Drugs
Unapproved Drugs Workshop
January 9, 2007

Regulatory Pathway: Abbreviated New Drug Application

Gary Buehler
Director
Office of Generic Drugs
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What are the requirements for a generic drug?

- Same active ingredient(s)
- Same route of administration
- Same dosage form
- Same strength
- Same conditions of use

Compared to reference listed drug (RLD)
- (brand name product)

Key Point -

In order to submit an ANDA, there must be a reference listed drug (RLD).

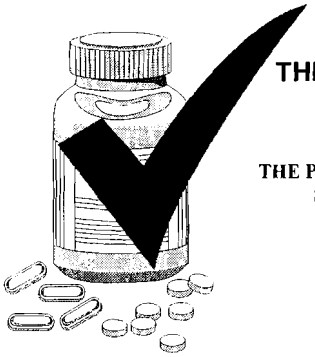
Listed drugs are found in FDA's

"Approved Drug Products with Therapeutic Equivalence Evaluations"

(the list; "Orange Book")

Reference products are denoted with a "+" in the Orange Book

APPROVED DRUG PRODUCTS



WITH
THERAPEUTIC EQUIVALENCE EVALUATIONS

22nd EDITION

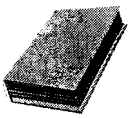
THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFORMATION TECHNOLOGY
DIVISION OF DATA MANAGEMENT & SERVICES

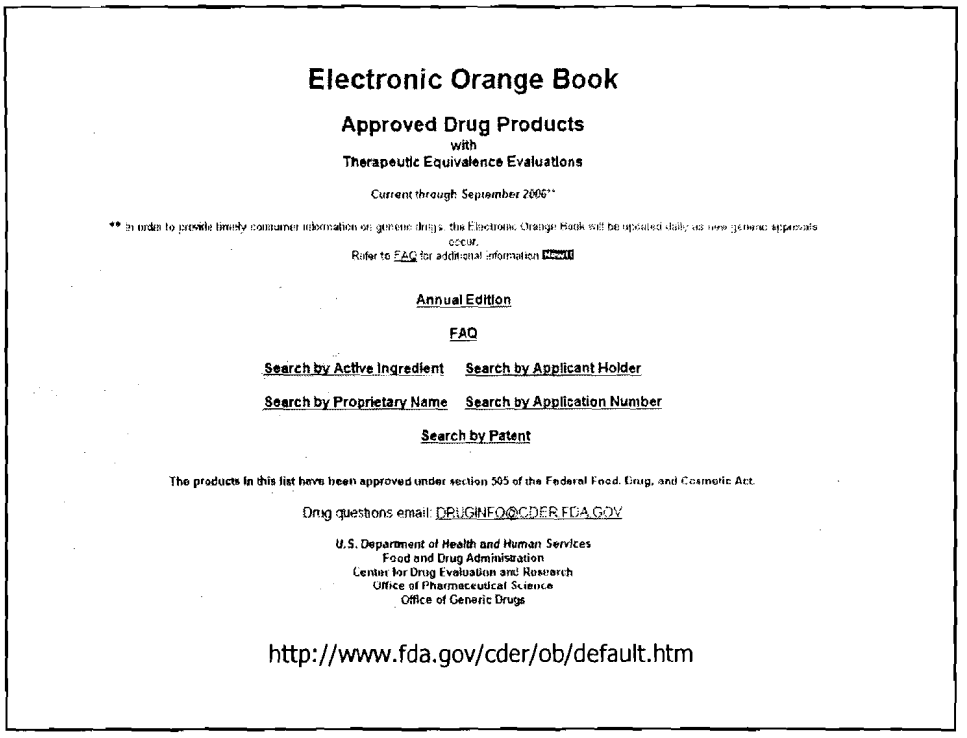
2002

Electronic Orange Book -
http://www.fda.gov/cder/ob/

"Orange Book"



- All FDA approved drug products listed (NDA's, OTC's & ANDA's)
  - Therapeutic equivalence codes
    - ➔"A" = Substitutable
    - ➔"B" = Inequivalent, NOT Substitutable
  - Expiration dates: patent and exclusivity
  - Reference Listed Drugs/brand drugs identified by FDA for generic companies to compare with their proposed products



Electronic Orange Book

Approved Drug Products
with
Therapeutic Equivalence Evaluations

*Current through September 2006***

** In order to provide timely consumer information on generic drugs, the Electronic Orange Book will be updated daily as new generic approvals occur.
Refer to FAQ for additional information

Annual Edition

FAQ

Search by Active Ingredient Search by Applicant Holder

Search by Proprietary Name Search by Application Number

Search by Patent

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Drug questions email: DRUGINFO@CDER.FDA.GOV

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science
Office of Generic Drugs

http://www.fda.gov/cder/ob/default.htm

Suitability Petition May Be Option

ANDA for product not identical to listed drug in:

- Route of Administration
- Dosage form
- Strength
- One active ingredient in a combination is substituted with another active
- PREA (21CFR314.93)

505(b)(2) NDAs Another Potential Option

Patent Certifications

The Act requires that an ANDA contain a certification for each patent listed in the Orange Book for the innovator drug. This certification must state one of the following:

I. that patent information relating to the innovator drug has not been filed;

II. that the patent has expired;

III. that the patent will expire on a particular date; or

IV. that the patent is invalid or will not be infringed by the manufacture, use, or sale of the drug for which approval is being sought.

Patent Certifications

- ✓A certification under paragraph I or II permits the ANDA to be approved immediately when otherwise eligible.
- ✓A certification under paragraph III indicates that the ANDA may be approved on the patent expiration date.

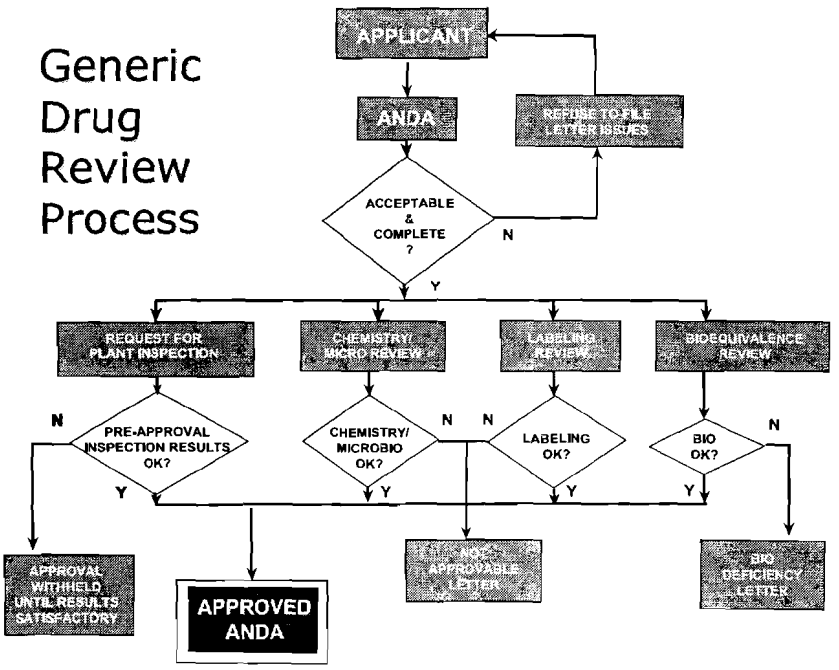
Patent Certifications

- ✓ A paragraph IV certification questions whether the listed patent is valid, enforceable, or will be infringed by the proposed generic product. The ANDA applicant who files a paragraph IV certification to a listed patent must notify the patent owner and the NDA holder for the listed drug that it has filed an ANDA containing a patent challenge. If either party files a patent infringement suit against the ANDA applicant within **45 days** of the receipt of notice, under most circumstances FDA may not give final approval to the ANDA for at least **30 months** from the date of the notice.
- ✓ The statute provides an incentive of **180 days** of market exclusivity to the "first" generic applicant who challenges a listed patent by filing a paragraph IV certification.

NDA vs. ANDA Review Process

Brand Name Drug NDA Requirements	Generic Drug ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies	
7. Clinical Studies	6. Bioequivalence
8. Bioavailability	

Generic Drug Review Process



Labeling

- "Same" as brand name labeling
- May delete portions of labeling protected by patent or exclusivity
- May differ in excipients, PK data and how supplied

Chemistry

- Components and composition
- Manufacturing and controls
- Batch formulation and records
- Description of facilities
- Specs and tests
- Packaging
- Stability

ANDA Stability and Batch Requirements

- 3 months of accelerated stability data must be submitted with the application
- Available room temperature stability data should also be included. An update on subsequent RT data will be requested during the review process
- One demonstration batch must be manufactured
  - Source of BE study product
  - Source of stability data
  - Complete batch record for this batch must be submitted

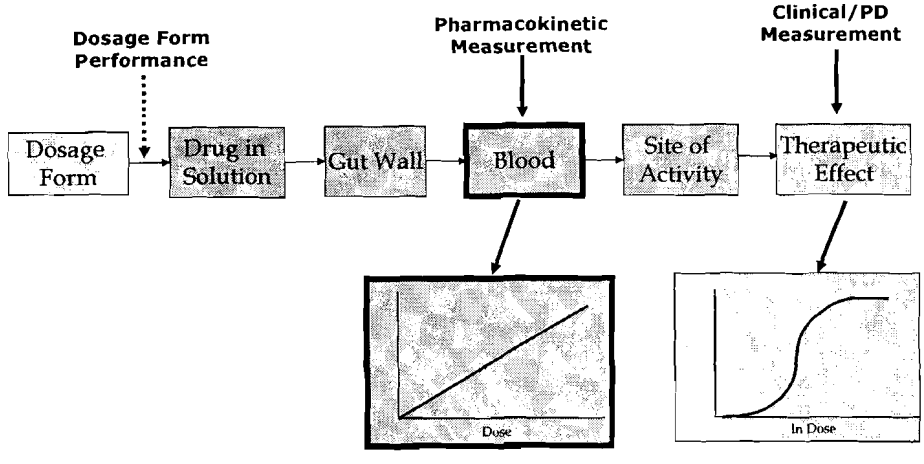
Definition of Bioequivalence

Pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions

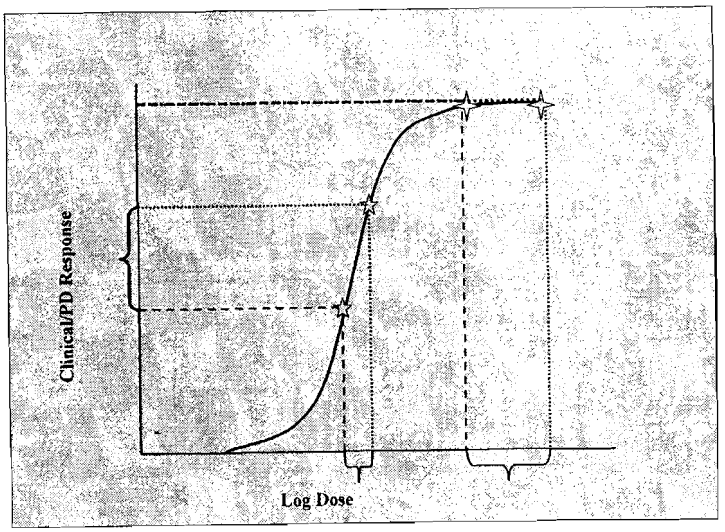
Purpose of BE

- Pharmaceutical equivalence + Bioequivalence = Therapeutic equivalence
- Therapeutically equivalent products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring
- The most efficient method of determining TE is to assure that the formulations perform in an equivalent manner

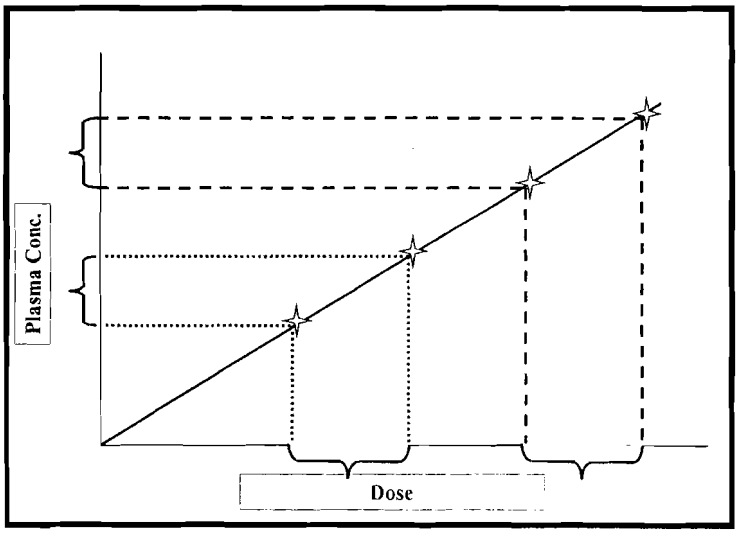
Model of Oral Dosage Form Performance



Clinical/PD Dose-Response



Plasma Concentration-Dose



Study Designs

- Single-dose, two-way crossover, fasted
- Single-dose, two-way crossover, fed
- Alternatives
  - Single-dose, parallel, fasted — Long Half-Life (wash-out): Amiodarone, Etidronate
  - Single-dose, replicate design — Highly Variable Drugs
  - Multiple-dose, two-way crossover, fasted — Less Sensitive: Clozapine (Patient Trials), Chemotherapy Trials
  - Clinical endpoint study — Topicals, Nasal Suspensions

Waivers of In Vivo Study Requirements

- Definition
- Criteria (21 CFR 320.22)
  - In vivo bioequivalence is self-evident
  - Parenteral solutions
  - Inhalational anesthetics
  - Topical (skin) solution
  - Oral solution
  - Different proportional strength of product with demonstrated BE

Statistical Analysis (Two One-sided Tests Procedure)

- AUC and Cmax
  - 90% Confidence Intervals (CI) must fit between 80%-125%

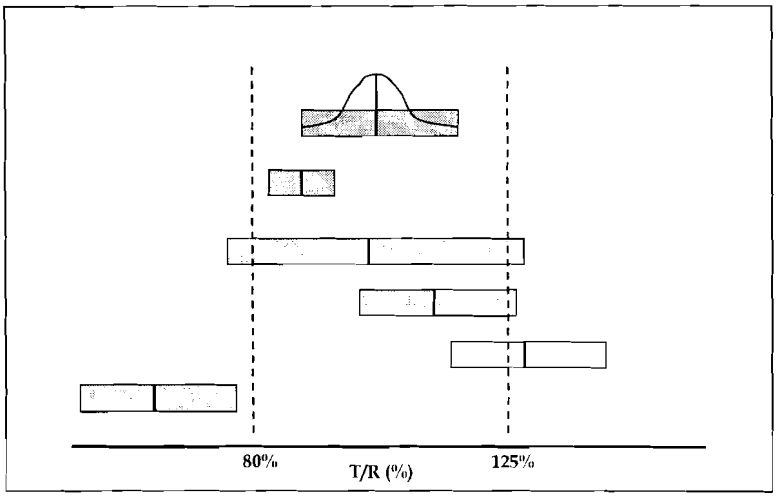
Statistical Analysis

- Bioequivalence criteria
  - Two one-sided tests procedure
    - Test (T) is not significantly less than reference
    - Reference (R) is not significantly less than test
    - Significant difference is 20% (α = 0.05 significance level)
      - T/R = 80/100 = 80%
      - R/T = 80% (all data expressed as T/R so this becomes 100/80 = 125%)

Statistical Analysis
80 - 125 %

- What does this mean?
- Can there be a 46% difference?
- What is a point estimate?
- What is a confidence interval?

Possible BE Results (90% CI)



Resources:

- Regulations
- Guidances
- Generic Pharmaceutical Association
- Several Consultant Firms
- Office of Generic Drugs
- OGD Website:
  http://WWW.FDA.GOV/CDER/OGD/

Regulatory Pathways: NDA Process

Kim Colangelo

Associate Director for Regulatory Affairs

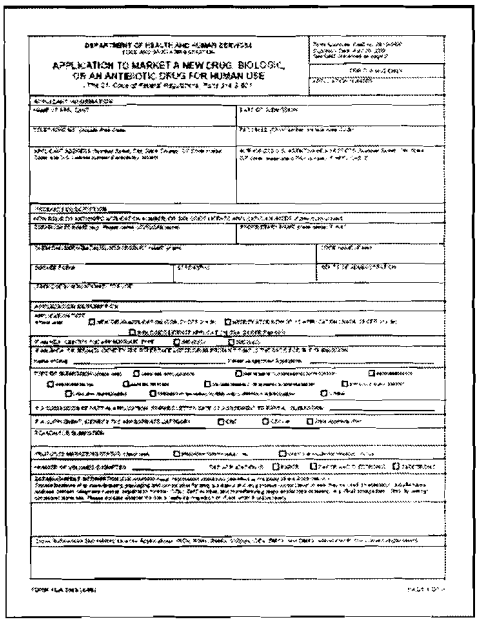
Office of New Drugs

Regulatory Pathways: NDA Process

Kim Colangelo
Associate Director for Regulatory Affairs
Office of New Drugs

What information is required for an NDA?

- Form 356h
  http://www.fda.gov/opacom/morechoices/fdaforms/cder.html



APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

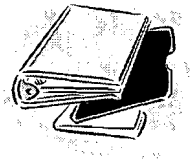
What information is required for an NDA?

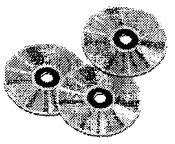
- Form 356h
  http://www.fda.gov/opacom/morechoices/fdaforms/cder.html
- Index
- Summary (including labeling, *marketing history*, technical sections)
- Technical sections (chemistry, nonclinical pharm/tox, human pharmacokinetics, statistical)
- Other (pediatrics, patent information, financial disclosure, etc.)

Code of Federal Regulations: 21 CFR 314.50
http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=200421

What is an acceptable format for an NDA?

- "Traditional" or "International" (Common Technical Document or CTD)
- Paper or Electronic or Mixed



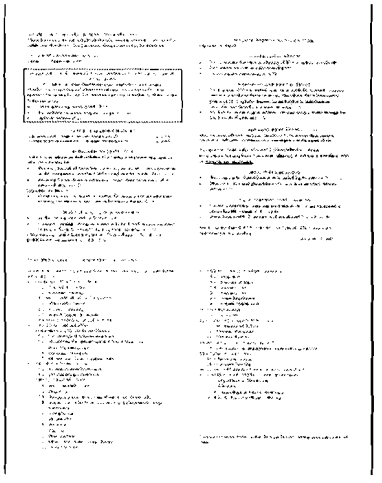


http://www.fda.gov/cder/about/smallbiz/default.htm

Did you know... Prescription labeling has a whole new look!

- Effective June 30, 2006, all new applications must be in the new format
  - Highlights
  - Table of contents

http://www.fda.gov/cder/regulatory/physLabel/default.htm



What is the difference between a 505(b)(1) and 505(b)(2) NDA?

- The standard for approval (substantial evidence of safety and effectiveness) is the same
- The *source* of data is different
  - 505(b)(1) – your data (you did the studies or you own the data) or you have right of reference (permission) to use the data
  - 505(b)(2) – relies upon data you don't own or have right of reference to, including published literature

What are some examples of products submitted as 505(b)(2) NDAs?

- Change from a previously approved drug in:
  - Dosage form
  - Formulation
  - Strength,
  - Route of administration
  - Dosing regimen
  - Indication
  - Active ingredient (e.g., different salt)

What are some examples of products submitted as 505(b)(2) NDAs?

- Substitution of an active ingredient in a combination product
- A combination of two previously approved products
- Monograph deviation

Guidance for Industry, Applications Covered by Section 505(b)(2)
http://www.fda.gov/cder/guidance/2853dft.htm
Response to Citizen Petition:
http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf

What makes a 505(b)(2) NDA "special"?

- It can rely upon "general" information (e.g., non-product specific published literature)
- It can rely upon our previous finding of safety and efficacy (i.e., a previously approved product)
  - Requires a scientific "bridge" to the approved product (generally a bioavailability or bioequivalence study)
  - Requires patent certification/statement

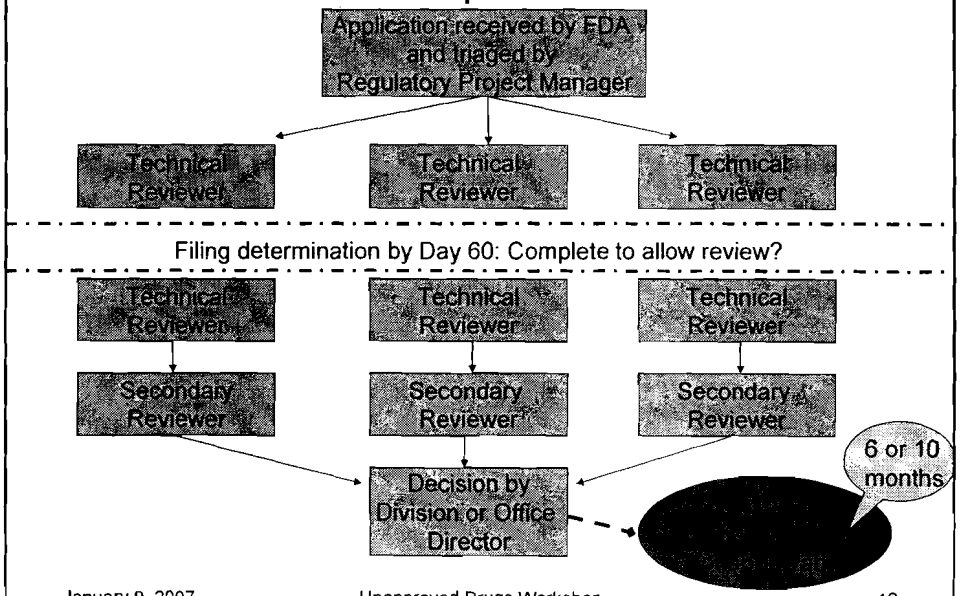
What is a patent certification or statement?

- Requires that the applicant of a 505(b)(2) application certify, to the best of their knowledge, to each patent that claims a drug relied upon to support approval of the (b)(2) product
  - Patent information submitted to FDA is found in the "Orange Book"

  http://www.fda.gov/cder/ob/default.htm
  - Types of patent certifications include not submitted, expired, will expire, etc...

  21 CFR 314.50(i)(1)(i)(A)

What is the review process for an NDA?



Some advice to the potential NDA applicant:

- Research available guidance documents
- Do a thorough literature search for information regarding the active ingredient in your product
- Request a meeting with the review division
  - Don't know which division?
    http://www.fda.gov/cder/cderorg/ond.htm

  Contact the Supervisory Regulatory Project Manager
  - Don't know how?
    Guidance: Formal Meetings With Sponsors and Applicants for PDUFA Products
    http://www.fda.gov/cder/guidance/2125fnl.htm

Thank you for your attention.

NDA/Demonstrating Product Effectiveness

Robert J. Temple, M.D.
Associate Director for Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Unapproved Drugs Workshop
January 9, 2007

NDA/Demonstrating Product Effectiveness

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Demonstrating Effectiveness

I will discuss the "harder" cases, where effectiveness is not established by:

- DESI effective rating
- Approved drug NDA
- Approved NDA or DESI combination containing the drug [we concluded that each component was effective]

In those cases bioavailability and chemistry are generally all that's needed for the same drug and possibly even for a different salt or ester (which, technically is a different drug but the same active moiety).

If the dosage form is different, studies may be needed (not for tablet/capsule; maybe for controlled release; certainly for most changes in route-inhaled, topical, but perhaps not all, such as injection "tide-over")

2

Demonstrating Effectiveness

If effectiveness of the active moiety is not established, approval requires that it be established. Generally the route for doing this is the NDA, whose effectiveness standard I will discuss.

Monographs (for OTC drugs) or seeking a determination of GRAE do not represent an escape. Effectiveness is established for drugs in a monograph more or less identically to NDA drugs.

GRAE is, if anything, a higher standard [Weinberger vs Hynson, Westcott, and Dunning: a consensus among experts. . . Based on published scientific literature of the same quantity and quality needed to approve a drug under section 505 of the Act].

3

Legal Standard

"New Drugs" must be shown effective under 505 (d)(5):

"substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."

"substantial evidence means evidence consisting of adequate and well-controlled investigations. . . By [qualified] aspects. . . on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect [represented in labeling]."

Note:
1. The interpreting experts are FDA
2. The effect has to be meaningful

[Warner-Lambert v Heckler, 1986]

4

Legal Standard

The plural in investigations was intended. FDAMA allows reliance on a single study plus "confirmatory evidence" but for symptomatic conditions it would be unusual for us to accept a single study. But the studies don't need to be identical and diverse sorts of data can provide support [Guidance: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998]

5

Legal Standard

The requirement is thus twofold:

- The supportive studies need to be "well-controlled"
- They need to be convincing

As a historical matter, two studies showing well-controlled, properly analyzed "statistical significance" (a 2-sided p-value of < 0.05) have been considered to be convincing to experts.

We have sometimes relied on a single stronger study, ($p = 0.01 - 0.001$) but usually for important outcomes.

6

Adequate and Well-Controlled Studies

21 CFR 314.126 gives the characteristics of an A&WC study. Briefly, they are

1. Comparison of the treatment with a control

   Because the course of most diseases, is variable, you need a control group, a group treated just like the test group, except that they don't get the drug, to distinguish the effect of the drug from spontaneous change, placebo effect, observer expectations.

7

Adequate and Well-Controlled Studies

1. Control (cont)

   The rule describes 5 kinds of control

   - Placebo
   - No treatment
   - Dose response
   - Active – superiority or Non-Inferiority
   - Historical

   For symptomatic conditions, randomization and blinding are needed and NI or historically controlled trials are unlikely to be persuasive.

   Therefore, placebo or dose-response are the usual designs needed.

8

Adequate and Well-Controlled Studies

2. Minimization of bias: a "tilt" favoring one group, a directed (non-random) difference in how test and control group are selected, treated, observed, and analyzed (the 4 main places bias can enter).

Remedies

- Blinding (patient and observer bias)
- Randomization (treatment and control start out equal)
- Careful specification of procedures and analyzes in a protocol to avoid
  - Choosing the most favorable analysis out of many (bias)
  - Having so many analyses that one is favorable by chance (multiplicity)

9

Adequate and Well-Controlled Studies

3. Sufficient detail to know how the study was done and what the results were

This was a major problem in the past and is definitely a problem if one is trying to rely on old literature. In those cases (still true today), analytic plan is rarely specified, handling of dropouts is rarely described, other therapy is not discussed. It is sometimes hard to tell duration of treatment and other critical details.

10

Adequate and Well-Controlled Studies

The basic principles were described in a 1970 rule, updated 1985, but we've learned a great deal, often from the DESI experience:

Just a few illustrations:

1. Interim looks at data
2. Counting all patients
3. Changing analyses
4. Active control non-inferiority trials
5. Having all the details

11

Interim Looks

If you monitor results as they come in, and stop when a goal is attained, you are likely to see "an effect" at some point, because of random variation, even if the drug does not work. We now know how to do this with appropriate correction, but we didn't always.

12

Interim Looks

Some people have known about the risks of interim looks, but let me tell you about cimetidine, the first H_2 blocker, approved in 1977

- 4 ulcer healing studies: C vs. placebo
  - 6 week
  - 4 week
  - 2 week X2
- Healing rates were monitored continuously (as each case was completed) and trials were stopped as soon as $p<0.05$; huge inflation of $\propto$ error
- The 2 wk studies worked out. The 4/6 wk studies were stopped but a few more cases wandered in, giving $p>0.05$

To my best knowledge, no one had ever raised the monitoring issue, at least for FDA submitted trials

13

Interim Looks

Perhaps it was the advent of outcome studies, procedures used in UGDP, BHAT, and growth of DMC's in the 1970's and 1980's but suddenly, by mid 80's or so, all were aware of an inflation and had remedies:

O'Brien-Fleming

Peto

Lan-DeMets, etc.

so everyone now knows you have to 1) correct for multiple looks at data, develop formal stopping rules, and, 2) avoid possible bias, e.g., by making adjustments of endpoints with knowledge of data (which interim efficacy evaluations could lead to), or modifying study design in other ways, such as by changing entry criteria.

BUT, old articles may not deal with this.

14

Counting All Patients

It seems obvious now, but if, at the end of a study, you can drop out patients for "good" reasons found after the study, you can make any study look favorable.

There were no FDA rules about this until a striking example, the ART (The Anturane Reinfarction Trial) showed us what could happen.

Now, in multiple guidance documents we ask for an accounting of all patients, or at least all patients with data. Any plans to drop anyone need to be specified.

Here's what the ART showed. It was an outcome trial but any study can be manipulated this way, and the omissions generally look very plausible.

15

Counting All Patients

The Anturane Reinfarction Trial, a study supported in the NEJM by two Dr. Braunwald editorials, seemed to show a survival benefit in post-AMI patients treated with sulfinpyrazone (Anturane), an anti-platelet drug. Our analysis taught us a lot: about cause-specific mortality, multiple endpoints, (unplanned 6 month analysis, unplanned cause-specific mortality analysis), but it was particularly important with respect to dropping patients [Temple R, Pledger G. The FDA's Critique of the Anturane Reinfarction Trial. N Engl J Med 303:1488-1492, 1980]

16

The Anturane Reinfarction Trial seemed a model effort, one of the first industry-sponsored outcome trials

17

Features of A.R.T.

Double-Blind (U.A. values hidden) - Shipped from C-G with numbers.

Randomized in blocks of 10 within each clinic

Placebo-Controlled

Patient Population
- Male or female
- Age 45-70
- AMI 25-35 days before
- ECG Documentation
- Typical Pain History

Enzymes: 2 of CPK, SGOT, LDH had to exceed 2X normal - 72 hr

No cardiomegaly, CHF >NYHA II, life-limiting disease

Baseline co-variates
- Index MI and later symptoms
- Smoking
- Medications
- Chest x-ray

18

A.R.T. REPORTED MORTALITY RESULTS

	Pl	S	% ↓ (p)
PATIENTS (Eligible)	783	775	
ALL DEATHS (analyzable)	62	44	29% (p=0.076)
CARDIAC D's	62	43	30.6 ~~32%~~ (p=0.058)
SUDDEN	37	22	43% (p=0.041)
AMI	18	17	--
OTHER	7	4	--
OTHER CV	0	1	--

19

MORTALITY by CAUSE, TIME

	Pl	S	% ↓ (p-value)
ALL CARDIAC	62	43	30.6% (p=0.058)
ALL CARDIAC			
0-6 M	35	17	50% (p=0.021)
7-24 M	27	26	
SUDDEN			
0-6 M	24	6	74% p=0.003)
7-24 M	13	16	
NON-SUDDEN			
0-6 M	11	11	
7-24 M	14	10	

20

Ineligible Patients

It was not possible to see this from published reports, but 9 patients who had died were excluded from the results (8 Anturane, one placebo) for being "ineligible" or having poor compliance (pills found in their room). When you put back exclusions, there was no documented effect.

21

TOTAL CARDIAC DEATHS

	P1	S
A.R.T.	62	43
POOR COMPLIANCE	1	2
LATE INELIGIBLE	0	6
LESS THAN 7 DAYS	5	4
INELIGIBLE <7D	1	0
TOTAL	69	55
		p=-0.2
LATE DEATHS	13	10
TOTAL	82	65
		p=0.162

22

Counting All Patients

FDA guidance and Medical Journal Guidance both now clearly call for an accounting of all patients.

It is very tempting to look at data and drop the "outliers," poor compliers, inappropriately entered, etc. It is even plausible. But if not rigorously planned it can be biased and, even if planned, can lead to imbalances that also introduce bias.

23

Changing Analyses/Multiple Analyses

In the ART, various plausible subanalyses were used, with no real attempt at statistical correction. We saw similar things in DESI. One I recall involved analyses in 2 pain studies

1. The overall studies showed no effect.
2. In study 1, an analysis of moderate and severe patients did show an effect.
3. In study 2, an analysis of mild patients showed an effect.

Subanalysis are possible but must be planned and with appropriate statistical correction.

24

Active Controls

A longer story than I can discuss here, but showing effectiveness by comparing 2 drugs and seeing "no significant difference," a once-common approach, is now well-understood to be of little use.

25

Interpretation of Active Control Trials

Active control equivalence or non-inferiority trials are an intuitively sensible alternative to the placebo-controlled trial, until you realize that effective drugs are not shown effective every time they're studied.

I remember exactly when I realized there was a problem, my epiphany: we saw proposed trials in 1978 or so that were going to compare nadolol with propranolol in angina. But we knew the large majority of placebo-controlled propranolol trials had failed (not shown any effect)

So, how could a finding of no difference between N & P mean anything at all?

It couldn't

26

Interpretation of Active Control Trials (cont.)

The non-inferiority trial tries to prove effectiveness by showing that the difference between the new drug (T) and the control (C), i.e., C-T, is less than some margin (M), which cannot be greater than the effect you know the control (C) had in this study. (If the difference is larger than all or the effect of C has been lost) But M is not measured (there's no placebo) so it must be assumed, based on past placebo-controlled trial experience. If you show statistically that

C-T<M (97½% CI lower bound)

Then T has some effect > 0

27

Interpretation of Active Control Trials (cont.)

The critical question is whether this trial could have distinguished the control from placebo and shown an effect of M. If it could have, the trial is said to have "assay sensitivity."

28

Assay Sensitivity

If a trial has assay sensitivity then if C-T < M, T had an effect. If the trial did not have assay sensitivity, then even if C-T < M, you have learned nothing

If you don't know whether the trial had assay sensitivity, finding no difference between C and T means either that, in that trial:

Both drugs were effective
Neither drug was effective

29

Assuring Assay Sensitivity In Non-Inferiority Trials - the Major Problem

In a non-inferiority trial, assay sensitivity is not measured in the trial. That is, the trial itself does not show the study's ability to distinguish active from inactive therapy. Assay sensitivity must, therefore, be deduced or assumed, based on 1) historical experience showing sensitivity to drug effects, 2) a close evaluation of study quality and, particularly important, 3) the similarity of the current trial to trials that were able to distinguish the active control drug from placebo

In many symptomatic conditions, such as depression, pain, allergic rhinitis, IBS, angina, the assumption of assay sensitivity cannot be made, as the following example shows.

30

TABLE 1. Results (4 week adjusted endpoint Ham-D total scores) of 6 trials comparing a new antidepressant, imipramine, and placebo showing only the new drug vs. imipramine comparison.

Study	Item	Common Baseline	NEW	IMI	"p" two tail	Power to detect 30% difference
R301	HAM-D	23.9	13.4	12.8	0.78	0.40
	(n)		33	33		
G305	HAM-D	26.0	13.0	13.4	0.86	0.45
	(n)		39	30		
C311(1)	HAM-D	28.1	19.4	20.3	0.81	0.18
	(n)		11	11		
V311(2)	HAM-D	29.6	7.3	9.5	0.63	0.09
	(n)		7	8		
F313	HAM-D	37.6	21.9	21.9	1.0	0.26
	(n)		7	8		
K317	HAM-D	26.1	11.2	10.8	0.85	0.33
	(n)		37	32		

31

TABLE 2. Results (4 week adjusted endpoint Ham-D total scores) of 6 trials comparing a new antidepressant, imipramine, and placebo showing all comparisons.

Study	Item	NEW	IMI	PBO	Baseline HAM-D adjusted
R301	HAM-D	13.4	12.8	14.8	23.9
	(n)	33	33	36	
G305	HAM-D	13.0	13.4	13.9	26.0
	(n)	39	30	36	
C311(1)	HAM-D	19.4	20.3	18.9	28.1
	(n)	11	11	13	
V311(2)	HAM-D	7.3	9.5	23.5	29.6
	(n)	7	8	7	
F313	HAM-D	21.9	21.9	22	37.6
	(n)	7	8	8	
K317	HAM-D	11.2	10.8	10.5	26.1
	(n)	37	32	36	

*IMI, NEW vs PBO, "p" less than 0.001

32

Active Controls

So you can use a non-inferiority design only where you can tell from historical experience that the control drug will almost always have a detectable effect of a defined size in a trial. As noted, few, symptomatic treatments will meet this test.

33

Number of Studies

As noted, 2 expected but FDAMA (1997) allowed 1 under some circumstances. A Guidance (1998) described cases in which this was reasonable and also addressed the issue of the Quality of evidence, less detached reports, literature, etc.

It described situations in which evidence from other sources (other studies or, sometimes, other drugs or pharmacologic studies, could support one new study of the drug.

34

One Study Plus Related Studies: Examples

A. Straightforward Cases of "confirmatory evidence" in the form of other adequate and well-controlled studies

1. Studies of different doses, regimens, dosage forms (may need no new study; if needed, generally only one). Anecdote: DESI history, entirely "proof of principle" (different doses, products, dosage forms, regimens, all examined together)

2. Studies in other phases of the same disease. Generally, expect similar direction of response in all stages, though magnitude and B/R may differ (typical in oncology, for same tumor; severities of heart failure)

3. Studies in other populations (if additional studies needed)

35

4. Combination and Monotherapy; each supports the other (typical in oncology, antihypertensives) - NB - not "automatic;" in one recent case, we did not conclude that an AED effective in combination was shown effective as monotherapy by a single favorable study: the effect was small and needed a larger dose; a second larger and longer study showed no effect.

5. Studies in a closely-related diseases or in pathophysiologically-related conditions: e.g., one study in each of two inflammatory conditions; one study in each of two pain models; anti-platelet drugs in acute coronary syndrome and post-PTCA

36

One Study Plus Related Studies: Examples

B. More difficult cases

6. Less closely related diseases, similar purpose of therapy. Effectiveness in one tumor might suggest reliance on a single study in a second tumor (possibly depends on tumor types); effectiveness of antibiotic at one site might support another setting with similar pathogens, at least in some sites

37

7. Studies with 2 different, but related clinical endpoints. Enalapril for CHF supported by one (of 2) exercise tolerance studies and one (dramatic) survival study; given both symptomatic and survival claims. Other examples could include different (but related) tests of depression or cognitive function, effects on survival and recurrent infarction in different studies.

   Issues: Suppose one endpoint is a surrogate; does it support an outcome claim (e.g., lipid-lowering drug with one outcome study and one study showing decreased coronary obstruction). This would seem to depend on amount of support for surrogate and existing outcome data. The surrogate could, of course, be considered "pharmacologic" evidence.

38

One Study Plus Related Examples

C. Most Difficult Case

8. Support by pharmacologic/pathophysiologic effect

NB: a) this is <u>not</u> the case of whether an accepted surrogate (these lead to ordinary approval) or a "reasonable" surrogate (these lead to accelerated approval), can be used as evidence. They can, although in both cases they generally do not lead to approval of an outcome claim. Could a surrogate be used to support a single study of outcomes?

b) few examples given because this is a treacherous area - there is always <u>some</u> pharmacologic effect; when is it confirmatory?

c) This is not the case where a single persuasive study is sufficient

Principle: "When the pathophysiology of a disease and the mechanism of action of a therapy are well understood, it may be possible to link specific pharmacologic effects to a strong likelihood of clinical effectiveness"

39

Pharmacologic Effect (cont'd)

Examples cited include:

- Replacement therapy, such as coagulation factor - clear evidence that deficiency leads to disease. Evidence of restoration of the missing physiologic activity provides support
- Correction of inborn effort of metabolism
- Vaccines: one clinical study plus animal challenge protection models, human serological data
- Caveats: Pharmacologic effects have misled (arrhythmia suppression, increased cardiac output by PDE inhibitors)

40

Pharmacologic Effect (cont'd)

Probably most sensitive case, because of potential broad applicability. Raises critical questions: 1) how much reliance do you place on clinical results with pharmacologically-related drugs; i.e., are the results with those other drugs "confirmatory evidence?" Do we have a "de facto" 1-study standard in this case in general or for serious outcomes? 2) how much weight does belief in mechanism carry; i.e., to what extent is that "relevant science" or "confirmatory evidence?"

Mortality/hospitalization in CHF. ACEI's (several) are effective. Other mechanism adverse

Is one not-overwhelming (but statistically significant) study with ACEI sufficient? Is one study of an angiotensin II inhibitor (probably same mechanism) sufficient? In fact, that has been the standard for ACEI's

41

Less Detail

Some degree of flexibility is described with respect to our usual level of submitted detail (i.e., everything) but there is clearly expressed concern about journals because their reviewers do not have all the data and peer reviewers are not all equal. But there are strengthening factors; generally some data, such as a protocol and a statistical analysis plan, randomization codes, etc.

42

Less Detail

Literature can be persuasive; the following increase the "possibility" that we could rely on it

1. Multiple well-designed studies by different investigators
2. Very detailed reports
3. Readily available and appropriate endpoints (not too much judgment)
4. Robust results by a protocol-specified analysis
5. Conducted by groups with track record

43

Public Workshop on Unapproved Drugs Preclinical Safety Requirements

January 9, 2007

David Jacobson-Kram, Ph.D., DABT
Office of New Drugs
Center for Drug Evaluation and Research
U.S. F.D.A.

Food and Drug Administration

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Examples of preclinical and nonclinical studies requested for an NME

- **Pharmacology (mechanistic and animal models, done in discovery, nonGLP)**
- **Safety pharmacology**
- **General toxicology**
- **Genetic toxicology**
- **Pharmacokinetics**
- **ADME (absorption, distribution, metabolism and excretion)**
- **Reproductive toxicology**
- **Carcinogenicity**
- **Special studies (e.g. juvenile)**

Why do we do ask for these studies?

- **Determine whether it is safe to put drug candidate into humans**
- **Determine what constitutes an initial safe dose for human clinical trials**
- **Help determine a safe stopping dose**
- **Identify dose limiting toxicities (what should be monitored in clinical trials)**
- **Assess potential toxicities that cannot be identified in clinical trials**

Waivers for Toxicology Studies

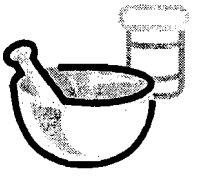
- For unapproved drugs that have been widely marketed (time and extent) certain tests can be waived.
- Single and repeat dose toxicology studies designed to evaluate acute and chronic effects can be waived because of clinical experience. These include general toxicology and safety pharmacology studies.
- Some toxicities cannot be readily identified from clinical experience. The need for such studies will be evaluated on a case-by-case basis.

What toxicities cannot be easily identified by clinical experience?

- Genetic damage – not generally assessed.
- Effects on fertility – hard to detect.
- Teratogenicity - high background rate of birth defects, however potent teratogens should be detectable epidemiologically.
- Carcinogenicity - high background, long latency period makes epidemiological studies insensitive, especially for common cancers.
- Data that address these toxicities may be available in the open literature. The need for studies to address these potential toxicities will by on a case-by-case basis.

Factors considered in requirement for carcinogenicity studies.

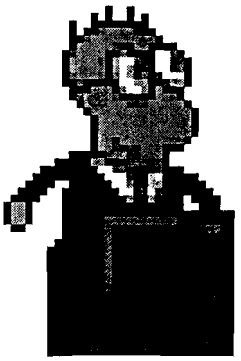
- **Continuous use is for six months or more. Used frequently in an intermittent fashion for chronic or recurrent conditions (allergic rhinitis, anxiety, depression).**
- **Cause for concern:**
  - **Genotoxicity**
  - **Product class**
  - **Structure Activity Relationships (SAR)**
  - **Evidence from repeat-dose studies, e.g. hyperplasia**



What if carcinogenicity studies are positive: Issues to consider

- What is the drug indication?
- Who is the target population? Geriatric, pediatric, obstetric.
- What is the likely duration of use?
- Are there other drugs already serving this medical need? What is their safety profile?
- What is the margin of exposure (carcinogenic vs. clinical dose)?
- Usually a labeling issue.

Thank you for your attention. Questions?



Workshop on Unapproved Drugs Demonstrating Clinical Drug Safety

January 9, 2007

Robert J. Meyer, MD

Director, ODE II / OND

Center for Drug Evaluation and Research

U.S. F.D.A.

Food and Drug Administration

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Demonstrating Drug Safety– Clinical Considerations

- For an New Molecular Entity (NME), one would want adequate data (controlled and uncontrolled) to allow for a risk-benefit determination
- ICH / FDA guidance asks for a minimum of the following for chronic use drugs indicated for non-life-threatening conditions:
  - 1500 patients exposed overall
  - Data from 300 patients for 6 months, 100 pts for 12 months
  - Extent needed, though, varies by circumstance ***(see Guidance on Pre-marketing Risk Evaluation: www.fda.gov/cder/guidance/6357fnl.htm)***

Demonstrating Drug Safety – Clinical Considerations

- Beginning question for an unapproved drug seeking approval is – what is already known and proven?
  - Has the drug moiety ever been approved (including final monograph or DESI review)?
    - In any indication?
    - In similar/same indication?
  - If not, how much information is known on the use of the drug?
    - Literature (RCTs, case series,...); anecdote

Demonstrating Drug Safety – Clinical Considerations

- If the drug substance was previously approved for the same or similar indication, reliance on previous findings of safety may be possible and would limit (if not negate) need for additional safety data
- If drug substance not previously approved or approval was for an unrelated indication, reliance on literature or other information may decrease amount of added safety data needed
  - If efficacy trials are needed, safety may be well supported, if not fully elucidated, by these trials

Demonstrating Drug Safety – Clinical Considerations

- Note, this advice refers to the active moiety. The drug is not made "different" by salts, esters, dosage form
- Information from the same active moiety from other manufacturers, or from the active moiety in other salts, esters, and/or dosage forms may provide some relevant for the safety assessment

Demonstrating Drug Safety – Clinical Considerations

- Questions for drug substances previously "approved" (including DESI/final mono.):
  - Same route?
  - Same duration / population?
  - Same (or less) exposure/dose?
- These questions will impact on what is "known," and what is "unknown" for proposed indicated use (and therefore needs to be demonstrated/studied)

Demonstrating Drug Safety – Clinical Considerations

- Important point: long-term marketing/use without prior approval and without available, useful data in the literature, may not provide much evidence of safety
  - Lack of defined Adverse Drug Reporting (outside of the Serious ADR reporting required since 1984)
  - Lack of controlled or even uncontrolled, systematic safety evaluations
  - Lack (often) of preclinical (animal) characterization of safety

Demonstrating Drug Safety – Clinical Considerations

- In summary, FDA needs assurance of safety to make decision on risk and benefit
- Risk decision making can be informed by previous findings from products with that drug substance and/or literature data on human (and animal) testing
- "Unknowns" left, after accounting for above, would need to be answered through clinical trials

Unapproved Drug Workshop Pediatric Studies

Lisa L. Mathis, M.D.
OND Associate Director
Pediatric and Maternal Health Staff
Office of New Drugs

9 January 2007

Unapproved Drug Workshop
Pediatric Studies

Lisa L. Mathis, M.D.
OND Associate Director
Pediatric and Maternal Health Staff
Office of New Drugs

9 January 2007

Objectives

- Describe legislation involving pediatric studies
- Describe voluntary study program
- Describe mandatory study requirements

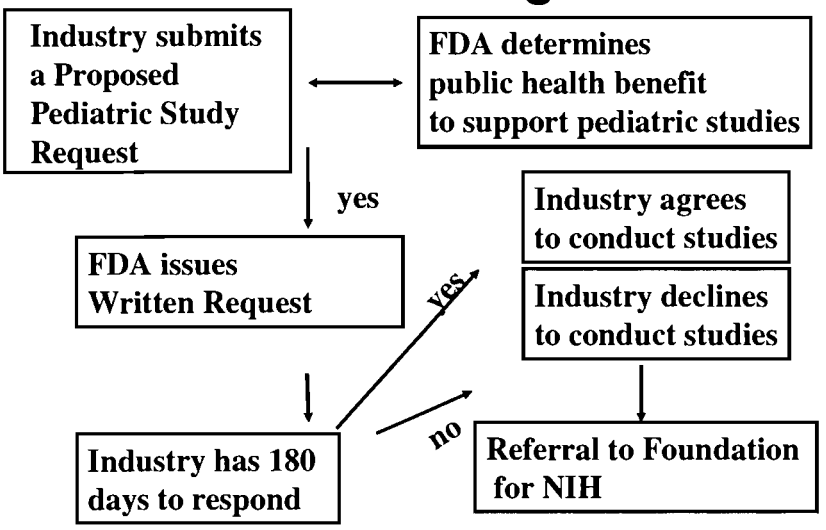
Pediatric Legislation

- Voluntary
  - Best Pharmaceuticals for Children Act
    - Signed into law January 4, 2002
    - Renewed pediatric exclusivity incentive originally in FDAMA
- Mandatory
  - Pediatric Research Equity Act
    - Signed December 3, 2003
    - Restored some important aspects from the Pediatric Rule, enjoined in 2002

Best Pharmaceuticals for Children Act (BPCA)

- Sponsor submits a Proposed Pediatric Study Request (PPSR) outlining proposed study and public health benefit of conducting such study in pediatric patients
- FDA may issue a Written Request (WR) for Pediatric studies
- If studies are performed per the WR, 6 months of exclusivity will attach to the entire moiety

Process for the Study of On-Patent Drugs



Pediatric Exclusivity

- 6 month period
- Attaches to existing patent or exclusivity
  - Not stand-alone exclusivity
- See "Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act " Guidance for Industry
  - http://www.fda.gov/cder/guidance/2891fnl.pdf

Pediatric Research Equity Act (PREA)

- Assessment required for applications:
  - New ingredient
  - New indication
  - New dosage form
  - New dosing regimen
  - New route of administration
- Waiver or deferral may be granted
- Guidance for Industry "How to Comply with the Pediatric Research Equity Act"
  - http://www.fda.gov/cder/guidance/6215dft.pdf

Pediatric Assessment

Assessment must contain:

- Data adequate to assess the safety and effectiveness of the drug or biological product, and
- Data to support dosing and administration for each subpopulation

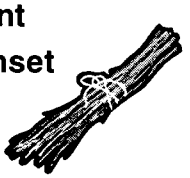
BPCA vs. PREA

BPCA

- Studies are voluntary
- Includes orphan drugs and orphan drug indications
- Drugs only
- Studies on whole moiety
- 10-1-07 Sunset

PREA

- Studies are required
- Orphan drugs designated exempt
- Biologics and Drugs
- Studies limited to drug/indication under development
- 10-1-07 Sunset



Conclusions

- Two pieces of pediatric specific legislation
- Sponsors submitting applications need to be familiar with the requirements and incentives
- While they do not apply to all drugs, make sure obligations and opportunities have been discussed with review division

Back up Slides

PREA Waiver Requirements

Waiver granted when:

- Necessary studies impossible or highly impracticable;
- Strong evidence suggests the drug or biologic would be ineffective or unsafe; or
- Product does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients

PREA Partial Waiver Requirements

Partial Waiver granted (applies to an age subset of the pediatric population) when:

- Same criteria as waivers but with additional requirement
- Reasonable attempts to produce a pediatric formulation necessary for that age group have failed

PREA Deferral Requirements

Deferral granted when:

- **Drug or biologic is ready for approval in adults;**
- **Additional safety and effectiveness data determined to be necessary; or**
- **There is another appropriate reason for deferral**

Patent and Non-Patent Exclusivities

Kim Dettelbach
U.S. Food and Drug Administration

January 2007

Patent and Non-Patent Exclusivities

Kim Dettelbach
U.S. Food and Drug Administration

January 2007

Patent Listings for NDAs

Section 505(b)(1)(G) and 505(c)(2) of the Federal Food, Drug, and Cosmetic Act (FFDCA)
Regulations at 21 C.F.R. 314.53

NDA sponsors file with FDA and FDA publishes (lists) patents that claim approved drug substances (active ingredients), drug products (compositions or formulations), or methods of use.

Patent Certifications

Sections 505(b)(2) and 505(j)(2)(A)(vii) of FFDCA
Regulations at 21 C.F.R. 315.50(i) and 314.94(a)(12)

ANDAs and 505(b)(2) applications referencing approved drugs must include certifications to listed patents for the drugs referenced.

Listed patents may delay subsequent ANDA and 505(b)(2) approvals.

Statutory Exclusivity vs. De Facto Exclusivity

- "De facto market exclusivity" referred to in Compliance Policy Guide (CPG) is different from statutory exclusivities
- De facto exclusivity in CPG refers to actual time on market without approved or unapproved competitors
- statutory exclusivities are bars on subsequent approvals and/or acceptance of future applications

Four Types of Statutory Exclusivity

Five Year New Chemical Entity Exclusivity

Three Year New Clinical Studies Exclusivity

Seven Year Orphan Drug Exclusivity

Six Month Pediatric Exclusivity

New Chemical Entity Exclusivity

Sections 505(c)(3)(D)(ii) and (j)(5)(D)(ii) of the FFDCA
Regulations at 21 CFR § 314.108

Granted to a drug that contains no active moiety that has been approved by FDA under section 505(b).

Active moiety is the molecule or ion … responsible for the physiological or pharmacological action of the drug substance.

NCE exclusivity runs from time of NDA approval and bars FDA from accepting for review any ANDA or 505(b)(2) application for a drug containing the same active moiety for

- five years if ANDA or 505(b)(2) does not contain a paragraph IV certification to a listed patent

- four years if ANDA or 505(b)(2) is submitted containing a paragraph IV certification to a listed patent

Three Year New Clinical Study Exclusivity

Sections 505(c)(3)(D)(iii) & (iv) and (j)(5)(D)(iii) & (iv) of the FFDCA
Regulations at 21 CFR § 314.108

Granted to drug when application or supplement contains reports of
new clinical investigations (not BA studies) conducted or sponsored by applicant and essential for approval

New clinical study exclusivity runs from time of NDA approval and bars FDA from approving, for a three year period, any ANDA or 505(b)(2) application that relies on the information supporting the approval of the drug or the change to the drug for which the information was submitted and the exclusivity granted.

Orphan Drug Exclusivity

Sections 526-527 of FFDCA
Regulations at 21 CFR §316

Orphan exclusivity granted to drugs designated and approved to treat diseases or conditions affecting fewer than 200,000 in the U.S. (or more than 200,000 and no hope of recovering costs).

Runs from time of approval of NDA or BLA.

Orphan exclusivity bars FDA from approving any other application (ANDA, 505(b)(2) or "full" NDA or BLA) for the same drug for the same orphan disease or condition for seven years.

Whether a subsequent application is for the "same" drug depends upon the chemical and clinical characteristics of the drugs.

FDA may approve applications for the "same" drug for indications not protected by orphan exclusivity.

Pediatric Exclusivity

Section 505A of FFDCA (FDAMA and BPCA)
No regulations
Guidance dated September 1999

Grants an additional 6 months of market protection at the end of listed patents and/or exclusivity for sponsor's drug products containing the active moiety, when the sponsor has conducted and submitted pediatric studies on the active moiety in response to a Written Request from FDA.

Pediatric exclusivity takes on characteristics of five year, three year or orphan exclusivity when it attaches to those protections.

It is not a patent extension when it attaches to a patent.

Prescription Drug User Fees

Unapproved Drug Workshop

January 9, 2007

Michael D. Jones

CDER's Office of Regulatory Policy

Prescription Drug User Fees

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PDUFA - 3 Kinds of Fees

- Application Fees (one time - when human drug application submitted)
- Product Fees (annual)
- Establishment Fees (annual)

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Fees

App Type	2007 Fee
IND	0
NDA w clinical data (CD)	$896,200
NDA: no CD	$448,100
Supp: w CD	$448,100
Supp: no CD	0

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Collection of Fees

- **Application Fees**
  - **No invoice; pay fee to Mellon Bank in Pittsburgh when application submitted; either need to have a waiver granted or must pay the fee when application submitted.**
- **Product and Establishment Fees**
  - **- Invoiced in August each fiscal year; payment due October 1**
  - **-"Clean up" bill in November**

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Bundling Policy and Definition of Clinical Data

- Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees (Dec. 2004)
  - what may be submitted in an application
  - what may be submitted in a separate application
  - what may be submitted as a supplement
  - provides a uniform definition of the term "clinical data" for user fees
  - provides a level playing field for industry

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Human Drug Application?

- "Human Drug Applications" assessed fees:
  - 505(b)(1) applications and certain biologics submitted under section 351 of the PHA
  - Most 505(b)(2) applications
  - b2's assessed fees if
    - new entity or
    - new "indication for a use" broadly interpreted
  - Not generic drug applications (505(j))

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505(b)(1) vs 505(b)(2)

- Key difference – who owns the data?
  - 505(b)(1) applications
    - you own or have the right of reference to data required for approval
  - 505(b)(2) applications
    - you do not own or do not have the right of reference to data required for approval

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Fee paying 505(b)(2)?

- Examples of new "indication for a use" include any change from application previously approved under section 505(b):
  - new indication
  - new patient population
  - new dosing regime
  - statements comparing to another product
- Once a 505(b)(2) application for a particular product is approved, subsequent applications will be submitted under 505(j) and will not be assessed fees under PDUFA

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Human Drug Application?

- "Human Drug Applications" do not include:
  - OTC Monograph Drugs (vs NDA OTC drugs)
  - ANDA's (a.k.a. 505(j)'s)
  - Investigational new drugs applications (INDs)
  - Drug Master Files (DMFs)
  - CBER carve outs (e.g., crude allergenic extracts)
  - Certain 505(b)(2)'s (those that are not new entities or new "indications for a use")
- Exemptions
  - Government applications IF not for commercial use
  - Orphan Exemption

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Waivers - 736(d) of the FDC Act

- Small Business
- Public Health
- Barrier to Innovation
- Fees Exceed the Cost

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Small Business

- First human drug application for you and your affiliates
- You and your affiliates have under 500 employees
- Full application fee waiver!

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Public Health – Barrier to Innovation

- Benefits public health or is innovative
- For example: priority review, NME, or fast track
- Also consider treatment alternatives
- Waiver "is necessary" or "because of limited resources"

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Fees Exceed the Cost

- All fees paid v. all costs!
- Guidance Document

  www.fda.gov/cder/pdufa/fecgud99.pdf
- Pay up front, but ....

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Annual Fees -- Products

- **The product must be**
  - **subject to an approved human drug application**
  - **in the active portion of the Orange Book**
  - **not the same as another product**
  - **not an OTC**
- **The applicant must have an application or supplement pending after 9/1/92.**
- **FY 07 fee = $49,750**

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Annual Fees -- Establishments

- The applicant, not the establishment owner, is responsible for the establishment fee
- Who must pay?
  - an applicant with applications or supplements pending after 9/1/92, who manufactures a *prescription drug product* in *final dosage form*
  - only if product is assessed a product fee
  - may share the establishment fee with others who use same manufacturing facility
- FY 07 Fee = $313,100

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Waiver Process

- Written request
- Courier to: Michael Jones, FDA/CDER/ORP, Rockwall 2, Suite 1101, 5515 Security Lane, Rockville, MD 20852
- Refer to pages 22 - 24 in FDA's Interim Guidance Document for Waivers of and Reductions in User Fees
- Call me once you have a draft and before you send in the request: 301-594-2041.

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WWW

CDER

http://www.fda.gov/cder/pdufa/default.htm

FDA

http://www.fda.gov/oc/pdufa/default.htm

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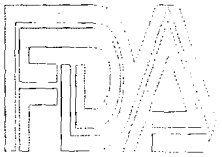
Unapproved Drugs Coordinator Role

Sally Loewke, M.D.
Assistant Director for Guidance and Policy
Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)

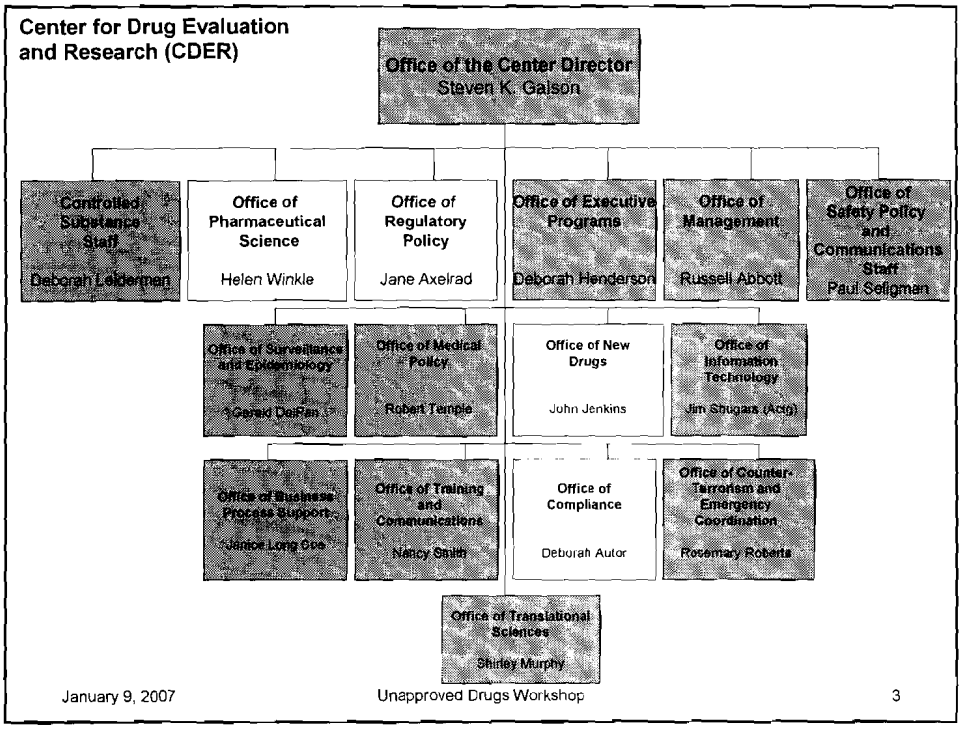


Unapproved Drugs Coordinator Role

Sally Loewke, M.D.
Assistant Director for Guidance and Policy
Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)

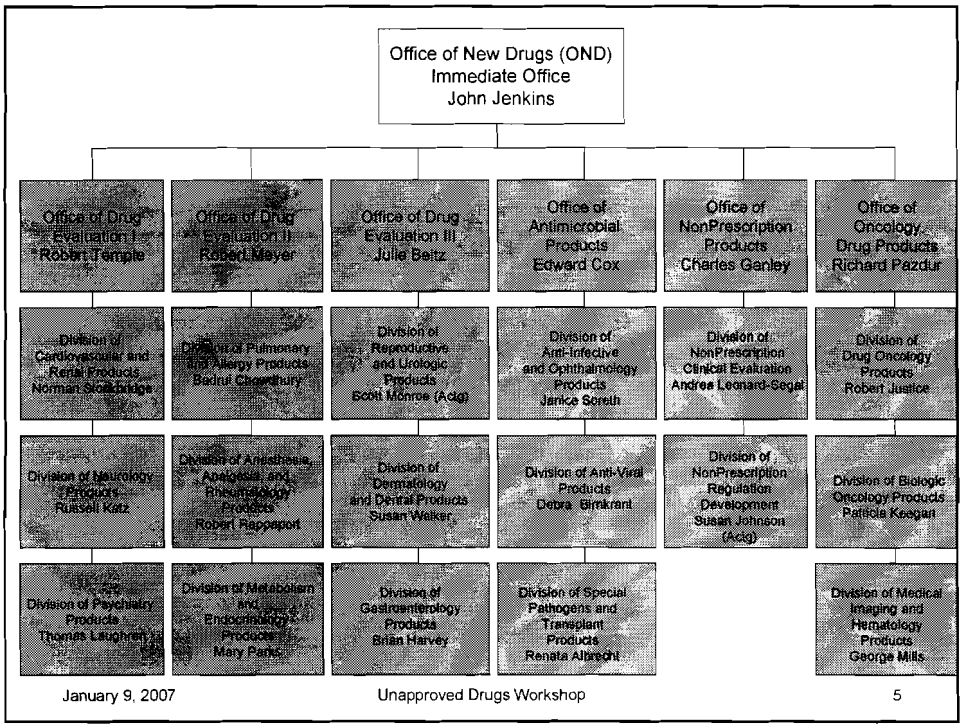
Unapproved Drugs coordinator

- Arose out of external inquiry about the potential inconsistencies in the application of review standards among Divisions within Office of New Drugs (OND) for marketed unapproved drugs
- Officially established in Dec. 2005
- Point of Contact for Center and OND



Duties

- **Center Level**
  - Act as a point of contact for Sponsors interested in pursuing an application
    - Provide contacts for appropriate Offices
      - Office of New Drugs
      - Office of Pharmaceutical Science
        - Office of Generics
      - Office of Regulatory Policy
        - User Fee Staff
      - Office of Compliance
        - Member of Compliance-led cross Agency unapproved drugs working group



Duties

- **OND Level**
  - Act as a point of contact for Sponsors interested in pursuing an application
  - Discuss general approach to getting started
    - Reviewing and summarizing the literature and any existing primary data
    - Requesting a pre-IND meeting with the appropriate OND Division
    - Providing contacts for appropriate OND review Divisions
  - Act as a liaison to the review Divisions to aid in consistency of OND's handling and response to requests for approval of marketed unapproved drugs
    - Interact with Divisions during the pre-meeting to help facilitate responses and identify any policy issues that may arise
    - Provide feedback and direction based on experiences in other Divisions
    - Update Divisions on related compliance actions

Industry Experiences

- Industry inquiries:
  - Where to start?
  - Who to submit to?
  - What studies are needed?
  - Do I have to pay User fees?
  - Clinical trial requirements?
  - Compliance guidance questions
    - Enforcement Discretion questions

OND Experience

- Briefing held or planned for
  - OND Office management
  - OND Division management
  - OND Reviewers
- Goal
  - Raise awareness
  - Raise and address policy issues
  - Standardize our approach across all Divisions

Workshop

- This workshop originated from the inquires received by the Office of New Drugs and the Office of Compliance
  - It was modeled after the type of frequently asked questions received
  - Intent was to give a broad look at the application process knowing that many Sponsors of unapproved drugs are small businesses with limited knowledge of the regulatory process
  - It is understood that each Sponsor will have different issues related to their drug product and those scientific issues should be directed to the relevant OND Division

Getting Started

- Review Guidances
- Review Literature
- Request a Pre-IND Meeting
- Meeting Package should include: 505(b)(2)
  - Review of the literature and a summary of the articles that are considered relevant to your application
    - Pharmacology/Toxicology
    - Clinical Pharmacology
    - Clinical Efficacy
    - Clinical Safety
  - Proposed Indication
  - Dose and Dosage form
  - Chemistry, Manufacturing, & Controls
    - Sufficient info to assure identity, strength, quality and purity

Contact Information

Sally.Loewke@fda.hhs.gov

301-796-0710